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ARYA Atherosclerosis

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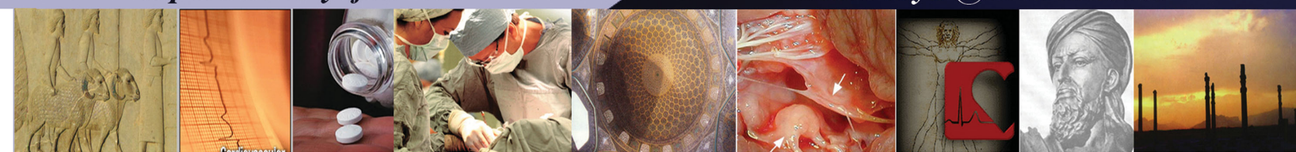
Serial Issue: 48 *Volume 11, Issue 4, July 2015* *Print ISSN: 1735-3955*
Online ISSN: 2251-6638



ARYA Atherosclerosis

Official Journal of the Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences

Publisher: Isfahan University of Medical Sciences,
Email: publications@mui.ac.ir

Copy Edit, Layout Edit, Design and Print: Farzanegan Radandish Co.
Tel: +98-311-2241953
+98-311-2241876
Email: f.radandish@gmail.com

Circulation: 500
Distribution: International
Language: English
Interval: Bimonthly
Print ISSN: 1735-3955, **Online ISSN:** 2251-6638

Address: ARYA Journal Office, Isfahan Cardiovascular Research Institute, Seddigheh Tahereh Research Complex, Khorram Ave. Isfahan, Iran
PO. Box: 81465-1148 Tel: +98-311-3377883 Fax: +98-311-3373435
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Table of Contents

The effects of occupational noise on blood pressure and heart rate of workers in an automotive parts industry

Saba Kalantary[(1)], Ali Dehghani[(2)], Mir Saeed Yekaninejad[(3)], Leila Omidi[(4)], Mitra Rahimzadeh[(5)]

Original Article

Abstract

BACKGROUND: One of the most important impacts of industrial noise is physiological and psychological effects. The increases in workers' blood pressure and heart rate were detected during and after exposure to high levels of noise. The objectives of this research were to determine whether the noise exposures have any effects on blood pressure and heart rate of workers in the automotive parts industry.

METHODS: This case study was done in 2011 at different units of an automotive parts manufacturing in Tehran. Sound pressure level was measured at different units of the factory with a calibrated instrument. Demographic features of workers were gathered with an appropriate questionnaire. Heart rate and blood pressure were measured twice in a day in the start time of work day (before exposure to noise) and middle shift hours (during exposure to noise) in the occupational physician office. For analyzing data, chi-square, independent sample t-test, paired t-test, and analysis of covariance (ANCOVA) were used. $P < 0.050$ was considered statistically significant.

RESULTS: The average age of workers in the case and control groups was 35.71 ± 8.10 and 33.40 ± 10.41 years, respectively. There was no difference between the average age of case and control groups ($P = 0.436$). The results of ANCOVA revealed the significant differences between the mean changes of heart rate $F_{(1, 37)} = 26.68$, $P < 0.001$, systolic blood pressure $F_{(1, 37)} = 21.70$, $P < 0.001$, and diastolic blood pressure $F_{(1, 37)} = 26.20$, $P < 0.001$ of workers in the case and control groups.

CONCLUSION: Exposure to industrial noise may increase the heart rate of workers. Although rises in heart rate, systolic, and diastolic blood pressure of workers in the case group were observed after exposure to noise, the values of heart rate, systolic, and diastolic blood pressure were in the normal range. Further experimental investigations are needed to determine the relationships between these variables.

Keywords: Occupational Noise, Exposure, Heart Rate, Blood Pressure, Industry

Date of submission: 4 Apr 2014, ***Date of acceptance:*** 6 Jun 2015

Introduction

Noise is classified as an unpleasant sound[1] that may cause stress among workers.[2] Noise exposure can decrease the quality of life.[3] One of the most important impacts of industrial noise is physiological and psychological effects. A progressive hearing loss is an important symptom of industrial noise exposure.[4] Acute and chronic exposures to loud noise may affect heart rate and blood pressure.[5] Chronic exposure to high sound levels may affect the human pathophysiological situation and can cause heart disease.[4] The increase in workers' blood pressure and heart rate has been detected during and after exposure to high levels of noise. During exposure to noise, endocrine systems known as stress indicators may change, and this change leads to an increase in blood pressure, heart rate, and the levels of stress hormones.[1,6] The positive correlation between exposures to occupational noise and increase in blood pressure was reported.[4]

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Noise exposure can disturb normal sleeping and lack of sleep is associated with decreased human performance, awareness, and mental capacity.[7] Some other physiological effects of noise include muscle cramps, dizziness, nausea, vomiting, and increased secretion of catecholamines and cortisol.[8] Noise induces heart disease and can cause hypertension.[9] Hypertension is a multi-cause heart disease and controlled by external and internal factors.[10] Some cross-sectional studies reported the association between noise as an external factor and increases in blood pressure and heart rate.[10,11] Hypertension has been seen in the cases occupationally exposed to the noise level of 100 A-weighted decibel scale.[10] The American Conference of Governmental Industrial Hygienists standard for industrial noise is 85 dBA.[12] Exposure to noise over 97 dBA can lead to physiological and mental changes in workers.[13]

The relationship between chronic noise exposure and hypertension among automotive assembly workers was investigated. Blood pressure was measured in 150 and 119 white and black men, respectively. Among studied workers, 22.0% of white and 31.9% of the black workers showed the symptoms of hypertension. Average diastolic blood pressure of workers was higher than 90 mm of mercury.[14] Some studies have also examined the effects of occupational noise exposure on blood pressure and heart rate of workers. There was no significant difference between the blood pressure and heart rate of steel industry workers before and after noise exposure (noise levels of 85, 95, and 105 dBA). Normal systolic blood pressure of participants increased after noise exposure, but no significant differences were found.[11] In another study, the effects of occupational noise exposure on changes in blood pressure of industrial workers were determined. Overall, noise exposure (97.5 ± 10.1 dBA) failed to affect the blood pressure and heart rate of workers.[10]

More recently, literature has emerged that offers contradictory findings about occupational noise exposure and its relationships with workers' blood pressure and heart rate.[4,11,15] The semi-experimental data are rather controversial, and there is no general agreement about the effects of industrial noise on heart rate and blood pressure of workers. The objectives of this research were to determine whether noise exposure affects blood pressure and heart rate of workers in the automotive parts manufacturing industry in Tehran, Iran.

Materials and Methods

This case study was done in 2011 at different units of an automotive parts manufacturing (Fan Avar Company) industry in Tehran. Exposed group members (cases) consisted of 26 workers who worked in various functional units of the industry. These workers with the age range of 20-56 years old had exposure to high levels of occupational noise (sound levels over 85 dBA). Sixteen unexposed office employees with the age range of 21-52 years were considered as control group. These employees were not exposed to high levels of occupational noise in their workplace (sound levels under 85 dBA).

Before the experiment was conducted, the workers' medical records were investigated. Workers with hearing problems, head injuries, hypertension, and other cardiovascular diseases were excluded from the study. All selected workers signed a consent form before participating in the research.

Sound pressure levels were measured at heavy pressing, manual pressing, cutting, metalworking lathe, and also administrative unit of the factory with a calibrated sound level meter (B&K model, Germany).

Demographic features of workers were gathered with an appropriate questionnaire. All workers occupationally exposed to high noise levels (noise levels over 85 dBA) with no previous history of heart disease were considered. Heart rate and blood pressure were measured twice in a day in the start time of work day (before exposure to noise) and middle shift hours (during exposure to noise) in the occupational physician office.[10] Heart rate monitor (PM80 Heart Rate Monitor Watch, Germany) was used to measure the workers' heart rate for 1 minute in the presence of the occupational physician. Blood pressure was measured twice at the workers right arms. After 5 minutes resting in order to minimize the adverse effects of some factors such as stress and activities,[1,10] the sphygmomanometer cuff (Model 1002/Presameter, Riester, Germany) was applied to measure systolic and diastolic blood pressure.[16] The measurements were done by a specially trained nurse. A normal systolic and diastolic blood pressure for human is 120-129 and 80-84 mmHg, respectively.[17] Human has the heart rate of 60-100 beat/minutes under normal resting conditions.[18]

Data were analyzed using SPSS software (version 18.0, SPSS Inc., Chicago, IL, USA). Numerical data were reported by mean and standard deviation (SD) and qualitative variables with frequency and percentage. Normality of numerical variables was tested by Shapiro-Wilk statistical method. The Chi-square test was applied to compare the proportions in several groups. Independent sample t-test was used to

compare the demographic and clinical factors between case and control groups at baseline noise levels. Analysis of covariance (ANCOVA) was used to determine the differences in the mean changes of response variables in case and control groups adjusting for work experience. Paired t-test was applied to inter-group comparisons. The result is significant at the $P < 0.050$.

Results

Eight workers (30.77%) were involved in the heavy pressing, 38.46% of them (10 workers) in manual pressing, 15.38% (4 workers) in cutting, and 15.38% of them (4 workers) in metalworking lathe unit. The noise levels during the work shift were in the range of 85-108 dBA.

The average and SD of age in the case group was 35.71 ± 8.10 years. The control group was in the average age of 33.40 ± 10.41 years. Table 1 shows the demographical features of workers in the case and control groups. Sample t-test showed no significant difference between the average age of case and control group members ($P = 0.436$).

Working experience of the case group was 60.73 ± 3.17 months. The working experience of the control group was 53.56 ± 3.72. Sample t-test revealed a significant difference between the average work experience in the case and control groups ($P = 0.002$). There were not significant differences in other demographical features of workers in case and control groups (Table 1). Mean body mass index (BMI) in the case and control groups was 23.16 ± 0.90 kg/m² (20.36-24.64) and 24.39 ± 0.62 kg/m². There was no significant difference in the mean BMI between the case and control groups ($P = 0.600$).

The results of independent samples t-test failed to show any significant differences in diastolic blood pressure ($P = 0.541$), systolic blood pressure ($P = 0.842$), and heart rate ($P = 0.681$) of workers in the case group before exposure to noise and baseline systolic and diastolic blood pressure levels and heart rate of workers in the control group (Table 1).

The results of paired t-test indicate that there was a significant difference between heart rate and diastolic blood pressure of all workers in the case and control groups before and after noise exposure ($P < 0.050$), but there were increases in systolic blood pressure of workers just in the case group before and after noise exposure. No increase in systolic blood pressure of workers in the control group was detected (Table 2).

Table 1. Comparisons between demographical features of workers and clinical factors before exposure to noise

Variables	Exposed group (cases) (n = 26)	Unexposed group (controls) (n = 16)	P
Age (year) (mean ± SD)	35.71 ± 8.10	33.40 ± 10.41	0.436*
Height (cm) (mean ± SD)	176.10 ± 9.40	173.40 ± 9.61	0.375*
Weight (kg) (mean ± SD)	71.90 ± 8.46	73.40 ± 7.83	0.569*
Months of work experience (mean ± SD)	60.73 ± 3.17	53.56 ± 3.72	0.002*
Diastolic blood pressure (mmHg)	76.17 ± 0.84	76.92 ± 0.73	0.541*
Systolic blood pressure (mmHg)	115.63 ± 1.00	115.91 ± 0.70	0.842*
Heart rate (bpm)	74.38 ± 1.20	75.19 ± 1.56	0.681*
High school education [n (%)]	15 (57.7)	4 (25)	
Bachelor of sciences [n (%)]	8 (30.8)	8 (50)	0.112**
Master's degrees [n (%)]	3 (11.5)	4 (25)	
Married workers [n (%)]	20 (77.0)	12 (75)	0.887**

* t-test; ** Chi-square; SD: Standard deviation

Table 2. Comparisons of heart rate and blood pressure of workers in the case and control groups

Groups	Sound pressure level (dB)	Parameters	Heart rate (bpm)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Unexposed group (controls)	53	Start time	75.19 ± 1.56	115.91 ± 0.70	76.92 ± 0.73
		Mid-shift	76.94 ± 1.18	116.39 ± 0.79	77.11 ± 0.63
		P (paired t-test)	< 0.001	0.280	0.026
Exposed group (cases)	85-108	Start time	74.38 ± 1.20	115.63 ± 0.99	76.17 ± 0.84
		Mid-shift	88.96 ± 6.80	127.31 ± 5.92	85.44 ± 3.74
		P (paired t-test)	< 0.001	< 0.001	< 0.001

The results of ANCOVA revealed the significant differences between the mean changes of heart rate $F_{(1, 37)} = 26.68$, $P < 0.001$, systolic blood pressure $F_{(1, 37)} = 21.70$, $P < 0.001$, and diastolic blood pressure $F_{(1, 37)} = 26.20$, $P < 0.001$ of workers in the case and control groups.

Discussion

The results showed that exposure to high level of noise may affect the heart rate, systolic, and diastolic blood pressure levels of exposed workers.

The mean of changes in heart rate of workers in the case group was 14 bpm from resting condition after noise exposure during the work shift. The results of ANCOVA revealed that there were significant differences in the mean changes of response variables (heart rate, systolic blood pressure, and diastolic blood pressure) between the case and control group members ($P < 0.001$). A rise in average systolic (11.68 mmHg) and diastolic blood pressure (9.28 mmHg) was observed in case group workers after exposure to 85-108 dB sound level.

Contrary to expectations, this study found that exposure to noise (53 dB) under recommended exposure standards may increase heart rate and diastolic blood pressure of workers in the control group. The results of the study did not show any significant differences between systolic blood pressure of workers in the control group in start time of work day and middle shift hours. The results indicate that significant rises in average systolic and diastolic blood pressure were found in the case group worker after exposure to noise compared with workers in the control group ($P < 0.001$). The findings of the current study are consistent with those of Kristal-Boneh et al. who found higher heart rate in workers exposed to higher noise levels.[5] These results are consistent with those of other studies and suggest that occupational exposure to noise may lead to increases in heart rate of workers.[19]

The results of the study showed that long time exposure to noise during a work shift have effects on heart rate, systolic blood pressure, and diastolic blood pressure of workers. It is encouraging to compare this figure with that found by Stansfeld and Matheson who found that exposure to high levels of noise can increase the systolic and diastolic blood pressure of workers.[20]

Overall, occupational exposure to noise in an automotive parts manufacturing industry affects workers' blood pressure in this study. The results of a cohort study was done by Sorensen et al. showed that a rise of 0.26 mmHg in systolic blood pressure was seen in participants exposed to road traffic noise levels.[21] The results of Neghab et al. study showed that occupational exposure to noise may increase the risk of hypertension in exposed group.[22] However, the results of some cross-sectional studies indicated that no significant differences were found between noise exposure and increases in blood pressure and heart rate of workers.[10,11] Although, the results of this study showed a significant effects of exposure to high levels of noise on increases in heart rate and blood pressure of workers, in all studied workers systolic and diastolic blood pressure were in the normal range of blood pressure criteria. The limitation of this study is that the mean of months of work experience in the case and control groups was significantly different ($P = 0.002$). Another limitation of this study was that the numbers of cases and controls were relatively small. Further research with adequate numbers of cases and controls is necessary to investigate the relation between occupational noise exposure and increases in heart rate and blood pressure of industrial workers. The use of hearing protection equipment can help to protect workers from adverse effects of occupational exposure to high levels of noise.[23] Workplace safety and health programs may have strong effects on reduction of injuries in workplaces.[24]

Conclusion

According to the results of the study, exposure to industrial noise may increase the heart rate of workers. Although rises in heart rate, systolic, and diastolic blood pressure of workers in the case group were observed after occupational exposure to noise, the values of heart rate, systolic, and diastolic blood pressure were in the normal range. Further experimental investigations are needed to determine the relationships between these variables.

Acknowledgments

The authors wish to thank the workers who participated in this study as well as managers of studied industry for their invaluable supports.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Kalantary S, Dehghani A, Yekaninejad MS, Omidi L, Rahimzadeh M. **The effects of occupational noise on blood pressure and heart rate of workers in an automotive parts industry.** ARYA Atheroscler 2015; 11(4): 215-9.

Development and validation of cardiac patient competence questionnaire, Iranian version

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Original Article

Abstract

BACKGROUND: The aim was to translate and develop a patient competence (PC) questionnaire in the context of cardiology and test its validity and reliability.

METHODS: In total, 148 cardiac patients who have inclusion criteria of the study were completed cardiac PC (CPC) questionnaire. Hospital Anxiety and Depression Scale and self-administered instrument European quality of life 5-dimensions were used to further validate the CPC questionnaire. The CPC was translated according to the recommended methodology for translating questionnaires, and psychometric properties including internal consistency, factor analysis, discriminant validity, construct validity, and concurrent criterion validity were tested.

RESULTS: Five domains in problem-focused task including search for information, self-regulation, being assertive, independent decision-making, and looking for social services, and three domains in emotion-focused task including stress management, confronting the threat, and avoidance were obtained by factor analysis. The standardized Cronbach's α of all domains were statistically significant ($P < 0.001$) and internal consistency for all domains was acceptable. Significant intercorrelations of CPC domains also indicated good criterion validity. As there were no cross-loadings, the domains have demonstrated good construct validity and discriminant validity.

CONCLUSION: The results of this study show that the Persian version of the CPC is a reliable and valid questionnaire. Although further improvement of this measure is clearly required, it suggests being a potential basis for investigating the determinants and health effects of CPC.

Keywords: Patient Competence, Cardiology, Reliability and Validity

Date of submission: 23 Jun 2014, ***Date of acceptance:*** 27 Jun 2015

Introduction

Research evidences reveal that involving patients in healthcare decisions has positive effect on healthcare outcomes.[1-3] Accordingly, patients should have skills, knowledge, and ability to make decisions.[4]

A review of the many scientific uses of the terms "competence" shows a variety of meanings: (a) all performance abilities and skills; (b) specific prerequisites necessary for acquiring primary knowledge systems; (c) learned knowledge and skills; (d) individual needs for effectiveness; (e) subjective evaluation of the self; and (f) the entire set of cognitive, motivational and social prerequisites for successful action.[5] Consequently, patient competence (PC) may be identified as patients' abilities or skills that enable them to solve tasks arising in the context of their illness and its treatment.[6]

To date, the concept of patient competencies have been rarely conceptualized in greater details. Although Giesler and Weis clarified a reliable instruments measuring PC in the oncological context that was contained problem and emotion-focused tasks of dealing with cancer,[7] measuring PC in other medical fields has not been concerned comprehensively.

According to the burden of cardiac disease, leading life-threatening conditions, reduced quality of life (QOL), variation in provision of types of

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medical treatment, and effects of emotions, feelings and social contexts,[8,9] patients with cardiac disease encounter several alternatives in their treatment process; thereby having ability and knowledge to make decisions on medical treatments and coping with cardiac disease are required.

Researches and practical experiences indicate that patients with chronic disease have become key decision makers in the treatment process. When patients have skill and knowledge about their condition, they will take some responsibilities for their disease management and get greater control on their lives.[10]

Thus, we want to clarify patient competencies construct conceptually and develop a questionnaire measuring patient competencies within a cardiology context and test its validity and reliability.

Materials and Methods

The translation and cross-cultural adaptation process for cardiac patient competence (CPC) were performed in agreement with best-practice methodology,[11] and the guideline for cross-cultural adaptation of self-report measures by Beaton et al.[12] and Paulsen et al.[13] and van den Akker-Scheek et al.[14]

An English 57-item self-rating measure of PC in oncology was translated into Persian by two independent Iranian native speakers who were fluent in English. A synthesis of the two questionnaires obtained was performed by an expert committee consist of two cardiologists and one psychiatrist. The expert committee revised the resulting Persian questionnaire based on cardiovascular parameters, some items such as "I am looking for information about signs and symptoms of cardiovascular disease," "I have a good deal of information about the importance of urgently going to the hospital when chest pain occurs," were added and some others revised based on these parameters for example, "I regularly check my weight and blood pressure myself," "I watch my healthy diet," "I have sought information on financial support and/or facilities that might be available for angioplasty and open-heart surgery," then questionnaire was back-translated into English by a bilingual English-native translator and the questionnaire obtained was evaluated by a new expert panel to determine cross-cultural adaptation, item relevancy, and content validity. Finally, a 63-item questionnaire was established in the context of cardiology.

The Persian version of CPC questionnaire was tested in fourteen patients who have at least 1-year diagnosis of acute coronary syndrome (ACS) and referred to cardiovascular clinics for treatment follow-up. After completing the questionnaire, the respondents were asked on the specific wording of each item, any difficulties in understanding the questions and their experience in answering the questionnaire. All respondents reported that the questions were understandable without any ambiguities, so the questionnaire did not require any indispensable changes.

Totally, 148 patients were enrolled in this study. They have at least 1-year diagnosis of ACS[15] (defined as acute myocardial infarction based on the World Health Organization Expert Committee and unstable angina by typical chest pain and dynamic electrocardiogram change confirmed by a cardiologist as ACS. The inclusion criteria were being 30-60 years of age and having no pregnancy or post-partum < 3 months, diabetes mellitus, arrhythmias, cardiac pacemakers, and heart failure.

To determine validity, three questionnaires were sent to all participants [CPC questionnaire, hospital anxiety and depression scale (HADS) and self-administered instrument European QOL 5-dimensions (EQ-5D)].

The CPC questionnaire was a 63-item, 5-point Likert scale with scores ranging from "not true at all" (1) to "completely true" (5). Factor analysis was prepared with principal component analysis (PCA), and the results were reviewed by an expert panel to determine item relevancy and content validity. Finally, 63-item questionnaire with 8 domains was established. The 63 items originally meant to describe the constructs of CPC questionnaire. All items were subjected to a principal components analysis with varimax rotation. Statistical criteria guiding the decision of a final component structure were the scree plot, eigenvalues > 1.0, percent of variance explained, and component loadings > 0.40.[16]

HADS was used for assessing depression and anxiety level of patients. It consists of seven items for anxiety and seven items for depression with scores ranging from 0 to 21. The higher scores indicate more intensity in anxiety or depression level. Scores > 7 in both domains indicate that participants are likely to be depressed or suffer from anxiety.[17,18] EQ-5D was used for detecting contributors QOL. Mobility, self-care, usual activity; pain/discomfort, and anxiety/depression were evaluated by this instrument. Three level of severity presented for each domain as 1 (no problems), 2 (some problems), and 3 (extreme problems). Global QOL score of participants was defined by the

combinations of dimensions' score. Higher EQ-5D scores indicate poor QOL.[19]

Data collection will be administrated by trained interviewer through face to face interview method. For this purpose, interviewer has been trained well, so that she is familiarized with how to fill the questionnaires and the ways of interviewing to prevent some of the common bias. Interviewer should be trained to make sure that the questionnaire is administered in a uniform way.

The study was approved by the Ethical Committee of Isfahan University of Medical Sciences, Iran, (grant number 191177). An informed written consent was taken from each participant.

Content validity of CPC questionnaire was confirmed by expert panel.

In addition for discriminant validity, the comparison group test was composed of depressed/non-depressed and anxious/non-anxious groups defined by HADS score. It was important to know whether the questionnaire could discriminate the population with depression and anxiety level. The two sample t-test was used for the comparison of depression and anxiety levels between depressed/non-depressed and anxious/non-anxious groups. To gain evidence for relationships between domains of CPC scale were tested using the Pearson correlation coefficient. Adequate factor discriminant validity is achieved when items relate more strongly to their own factor than to other factors. When testing the association of an item with its corresponding factor, a correlation coefficient > 0.7 indicates undesired shared variance between factors.[20] Discriminant validity of the questionnaire were between 0.4 and 0.6 for all domains. The correlation between domains of questionnaire and total score of HADS and EQ-D5 confirmed concurrent criterion validity.

For reliability, internal consistency was examined. With regard to internal consistency, the homogeneity of the question items in each domain was evaluated using Cronbach's α coefficient. A coefficient of 0.7 or higher is preferred for a questionnaire to be internally consistent.[21,22] The deletion of any single item did not meaningfully impact alpha. The 95% confidence interval was declared for Cronbach's α. The factor analysis in the construct validity confirmed the internal consistency. Data were analyzed using SPSS software for Windows (version 15, SPSS Inc., Chicago, IL, USA).

Results

In this study, 148 of the total completed questionnaire were useable. Of the all participants, 79 (53.4%) were male and 69 (46.6%) were female. The mean age of them was 53.63 ± 5.15. 123 (83.1%) were married. The mean year of education was 7.18 ± 5.71. Of all participants, 31 (20.9%), 59 (39.9%), and 58 (39.2%) were employer, housewife, and retired, respectively.

At first, factor analysis was prepared with PCA, to cluster questions in defined groups and the results were reviewed by expert panel. Five factors referring problem-focused and three factors referring emotion-focused aspects of CPC were extracted by factor analysis that had allocated themselves the 45.93% of variance. According to the content of questions, we named each derived factors that adjusted to our presumptions. It confirmed construct validity.

In problem-focused aspect, there were 11 items under the search for information domain, 14 items under the self-regulation domain, 7 items under the being assertive domain, 7 items under the Independent decision-making domain, and 2 items under the looking for social services domain. In the aspect of emotion-focused, 10 items under the stress management domain, 6 items under the confronting the threat domain, and 6 items under the avoidance domain were exist (Table 1).

The mean score of stress management search for information, self-regulation, and confronting the threat domains were significantly higher in the non-depressed group. In a non-anxious group, stress management and self-regulation mean scores were significantly higher. It has been carried out for discriminant construct validity (Table 2).

According to the findings, search for information domain was statistically correlated with other domains of CPC questionnaire except stress management. Correlation of other domains of CPC questionnaire has been shown in table 3.

Concurrent criterion validity of the CPC questionnaire was computed by correlating the total scores of each domain with HADS and EQ-D5. According to the results shown in table 4, some domains of CPC questionnaire had significantly negative relation with depression, anxiety, and QOL. Cronbach's α coefficient ranged from 0.554 to 0.831 for each domain indicating acceptable internal consistency. The deletion of any single item did not meaningfully impact alpha. Table 5 shows the Cronbach's α of all domains.

Table 1. Factor analysis of cardiac patient competence (CPC) questionnaire

Number	Item	Loading factor
1. Stress management (10 items) (eigenvalue = 8.45, accounted for 13.42% of variance)		
PC42	I can cope with feelings of helplessness	0.763
PC43	I am confident it all ends well	0.535
PC44	I can overcome my fears of disease	0.692
PC45	I can cope with stress of undergoing angiography or angioplasty	0.614
PC46	I can ignore thoughts of recurrence of my disease	0.675
PC47	I can cope with problems arising from my disease	0.749
PC48	I can cope with disabilities caused by my disease	0.754
PC49	I can manage emotions like sorrow, fear and anger arising from disease	0.557
PC50	When I am stressed by thoughts of my disease, I manage to distract myself by other thoughts	0.392
PC51	I think of my disease and say “things could have been worse”	0.777
2. Search for information (11 items) (eigenvalue = 6.46, accounted for 10.25% of variance)		
PC1	I am looking for information about diagnostic methods	0.810
PC2	I am looking for information about side effects of invasive diagnostic methods	0.761
PC3	I am looking for information about treatment in brochures, books, etc.	0.677
PC4	I have prepared myself for stressful diagnostic procedures in the future	0.363
PC5	I am looking for information about prevention of cardiovascular diseases, such as a healthy diet, adequate physical activity, smoking cessation, and stress management techniques	0.397
PC6	I have asked doctors about various therapeutic methods and the differences between them	0.588
PC7	I am looking for information about recurrence and survival of cardiovascular disease	0.743
PC8	I have obtained comprehensive information about positive and negative aspects of various therapeutic methods and medications	0.673
PC9	I am looking for information about signs and symptoms of cardiovascular disease	0.672
PC10	I have a good deal of information about the importance of urgently going to the hospital when chest pain occurs	0.626
PC11	I have obtained enough information about doing my personal tasks following cardiovascular disease such as driving, back to work, etc.	0.720
3. Self-regulation (14 items) (eigenvalue = 2.85, accounted for 4.53% of variance)		
PC12	I am sure others can help me	0.617
PC13	I talk to my family and loved ones about the extent of support I need	0.785
PC14	It’s easy for me to ask for other’s support	0.671
PC15	I draw comfort from the attention my loved ones pay to my disease	0.582
PC16	I am looking for ways of coping with stress and problems of daily living	0.415
PC17	I watch my healthy diet	0.803
PC18	I take care to get enough rest enough and stay stress-free	0.580
PC19	I regularly check my weight and blood pressure myself	0.370
PC20	There’s always time in my life for contemplation	0.478
PC21	I watch out for signs and signals from my body	0.396
PC22	I have sought information on things which are harmful for my disease and I should avoid	0.445
PC23	I see my doctor for regular check-ups	0.692
PC24	I am looking for ways to help me stop smoking cigarettes, hookah, and substance	0.764
PC25	I try to get enough exercise	0.462
4. Being Assertive (7 items) (eigenvalue = 2.58, accounted for 4.10% of variance)		
PC26	I find it difficult to accurately describe my problems to physicians (reverse scoring)	0.355
PC27	I openly speak to my doctor about treatment methods I dislike	0.746
PC28	I usually get my doctor to agree to my preferences on how to go about having a treatment	0.749
PC29	I tell my doctor when I am not happy with the treatment method he/she has suggested	0.762
PC30	When my doctor says something I do not understand, I ask for clarification	0.716
PC31	I manage to ask my doctor all my questions	0.630
PC32	I find it difficult to discuss my thoughts and ideas with my doctor (reverse scoring)	-0.742
5. Independent decision-making (7 items) (eigenvalue = 2.40, accounted for 3.80% of variance)		
PC33	I have dedicated some time to finding the best treatment method	0.497
PC34	I succeeded in arriving at a decision that was right for me	0.453
PC35	I have consulted other doctors and sought their opinion in making treatment decisions	0.613
PC36	I was skeptical about treatments suggested by physicians	0.705
PC37	I left decisions concerning my treatment to the physicians	0.545
PC38	I have sought information on unconventional therapies (alternative medicine/traditional medicine)	0.737

Table 1. Factor analysis of cardiac patient competence (CPC) questionnaire (Continue)

Number	Item	Loading factor
PC39	I have spoken to an alternative medicine specialist (Homeopathy, Chinese medicine, and vegetarianism) about my disease	0.787
6. Looking for social services (2 items) (eigenvalue = 2.25, accounted for 3.58% of variance)		
PC40	I have sought information on financial support and/or facilities that might be available for angioplasty and open-heart surgery	0.765
PC41	I have sought financial and/or insurance support in relation to my disease	0.755
7. Confronting the threat (6 items) (eigenvalue = 2.01, accounted for 3.19% of variance)		
PC52	I confront symptoms of recurrence and exacerbation of my disease head on	0.409
PC53	I think of what my disease means for my future	0.709
PC54	I think that death is always a possibility in my situation	0.671
PC55	I try to take good care of myself	0.752
PC56	I know how to deal with exacerbation of my disease symptoms	0.569
PC57	I can cope with my physical and movement disabilities	0.391
8. Avoidance (6 items) (eigenvalue = 1.93, accounted for 3.06% of variance)		
PC58	I find it hard to discuss my needs and requirements with others	0.560
PC59	I feel I must radically change my life based on my disease	0.356
PC60	I find it hard to come to terms with my disease	0.681
PC61	I won't allow others to know how I feel	0.734
PC62	I participate in various activities to forget my disease	0.670
PC63	I comfort myself by thinking of people who are worse off than myself	0.510

PC: Patient competence

Table 2. Scores of all domains of the cardiac patient competence (CPC) based on depression and anxiety level

Domain	Depression		P	Anxiety		P
	Depressed	Non-depressed		Anxious	Non-anxious	
Search for information	26.91 ± 9.84	30.45 ± 9.85	0.040	28.81 ± 10.34	29.27 ± 9.72	0.790
Self-regulation	51.26 ± 8.94	55.94 ± 7.24	0.001	52.23 ± 8.92	55.58 ± 7.49	0.020
Being assertive	20.31 ± 5.40	20.65 ± 4.63	0.690	20.90 ± 5.34	20.17 ± 4.66	0.380
Independent decision-making	18.14 ± 5.41	19.31 ± 5.51	0.210	19.34 ± 5.68	18.47 ± 5.31	0.340
Looking for social services	5.91 ± 2.58	6.18 ± 2.19	0.500	5.74 ± 2.52	6.39 ± 2.16	0.090
Stress management	31.96 ± 9.30	40.96 ± 6.34	< 0.001	32.83 ± 8.97	40.97 ± 6.91	< 0.001
Confronting the threat	21.24 ± 5.18	23.36 ± 4.28	0.009	21.85 ± 5.19	23.16 ± 4.19	0.090
Avoidance	18.65 ± 4.28	17.76 ± 4.16	0.220	18.73 ± 4.34	17.69 ± 4.07	0.140

Table 3. Pearson's correlations of the cardiac patient competence (CPC) questionnaire domains

Domain	1	2	3	4	5	6	7	8
1. Search for information	1							
2. Self-regulation	0.407**	1						
3. Being assertive	0.216**	0.145	1					
4. Independent decision-making	0.552**	0.203*	0.244**	1				
5. Looking for social services	0.269**	0.037	0.105	0.240**	1			
6. Stress management	0.019	0.283**	-0.004	-0.013	0.046	1		
7. Confronting the threat	0.275**	0.515**	0.119	0.136	0.218**	0.374**	1	
8. Avoidance	0.254**	-0.009	0.041	0.091	0.124	-0.084	0.260**	1

* Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed)

Table 4. Pearson's correlation coefficients (r) between the cardiac patient competence (CPC) questionnaire domains and European quality of life 5-dimensions (EQ-5D) and hospital anxiety and depression scale (HADS) questionnaires score

Domain	Quality of life	Depression	Anxiety
Search for information	-0.169*	-0.174*	0.072
Self-regulation	-0.176*	-0.296**	-0.227**
Being assertive	-0.054	-0.049	0.053
Independent decision-making	-0.097	-0.111	0.105
Looking for social services	-0.091	-0.203*	-0.074
Stress management	-0.397**	-0.515**	-0.630**
Confronting the threat	-0.211*	-0.225**	-0.215**
Avoidance	-0.015	0.019	0.181*

* Correlation is significant at the 0.05 level (2-tailed); Correlation is significant at the 0.01 level (2-tailed)

Table 5. Internal consistency of the cardiac patient competence (CPC) questionnaire

Domain	Cronbach's alpha*
Search for information	0.831
Self-regulation	0.796
Being assertive	0.744
Independent decision-making	0.694
Looking for social services	0.554
Stress management	0.803
Confronting the threat	0.792
Avoidance	0.687

* P < 0.001

Discussion

This study attempted to clarify patient competencies construct conceptually and develop a questionnaire measuring patient competencies within a cardiology context and test its validity and reliability. As data analysis shows different domains of CPC in problem and emotion - focused tasks were derived.

Since patients dealing with the problems related to life-threatening illness such as cardiovascular disease need information, those who often lack knowledge about their condition and prognosis may contribute to depression, poor drug adherence, unplanned admissions, and less decision-making involvement.[23] Thus, searching information about their disease is considered to promote their understanding of the recommended therapies and behavior changes[24] and make sure that they know the risk and are informed about how to reduce it.[25]

Effective regulation may facilitate one's ability to concentrate and solve illness problems. Accordingly, self-regulation has been identified as a healthy psychological asset that enables individuals to regulate what they feel and do. We have some evidence in hand that effective self-regulation reduces chronic distress and enhances positive emotional experience.[26]

The assertive aspects of extraversion that prompt individuals to seek and retain social dominance might, therefore, increase cardiovascular morbidity, possibly via the psychosocial stress associated with maintaining dominant social relations.[27,28]

In order to patients have a right to achieve their goals, be satisfied and adhere to treatment, independent decision making can help them to reach what they want and await[29] and contribute to a better state of health.[30]

According to the result of some study, treatment and control of the disease are lower among uninsured adults. Increasing the portion of insured individuals may be progress the treatment and control of cardiovascular disease risk factors and make a reduction in health disparities.[31]

Additionally, patients are concerned of their future life, dealing with disease symptoms, coping with disease complication, and difficulties on expressing their feelings. These are emotional aspect of CPCs. Due to an important role of emotion as a trigger for acute coronary events.[32,33] There have been several prospective studies of stress and emotion as probable risk factors for cardiovascular disease. This new understanding is in agreement with the view that emotional processes are risk factors for cardiovascular disease.[9,34] Consequently, managing stress, confronting with the threat of disease and using the way of expressing feelings will have been required.

In short, the first Persian version of the self-rating measure of PC in the context of cardiology is reliable and valid, and provides a basis for future research. Although some improvement is needed, we are expecting that enhancing reliability and construct validity of this questionnaire will finally tend to appear tools for measuring patients' strength and weaknesses in dealing with cardiology, help to better make decision and design and evaluate interventions to enhancing it.

The limitation of our study was that we do not have a gold questionnaire for comparison of our CPC questionnaire. The CPC was developed in Persian, since it does not contain items that are specifically related to Iranian culture, it could be translated and used internationally.

Acknowledgments

This study was supported by the Isfahan University of Medical Sciences grant No: 191177. We gratefully acknowledge Jurgen M. Giesler and Joachim Weis for their kind cooperation. Also, we would like to gratitude interviewer and all participants who helped us in performing this study.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Roohafza H, Sadeghi M, Khani A, Afshar H, Amirpour A, Sarrafzadegan N, et al**. Development and validation of cardiac patient competence questionnaire, Iranian version.** ARYA Atheroscler 2015; 11(4): 220-27.

Comparison of N-acetylcysteine, ascorbic acid, and normal saline effect in prevention of contrast-induced nephropathy

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Original Article

Abstract

BACKGROUND: Considering the crucial role of appropriate preventative strategies in reducing the rate of contrast-induced nephropathy (CIN) occurrence and its related morbidity and mortality, the effect of N-acetylcysteine (NAC), ascorbic acid (AA), and normal saline (NS) was investigated in the patient's undergone coronary angiography.

METHODS: In this clinical trial, 120 patients scheduled for elective coronary angiography with serum creatinine (Cr) level > 1.5 mg/dl or glomerular filtration rate (GFR) ≥ 60 selected by convenience method. Selected patients were allocated in three treatment groups randomly to receive oral NAC (600 mg/twice daily) plus NS (100 ml/hour) (Group A), oral AA (250 mg/twice daily) plus NS (100 ml/hour) (Group B) and NS (100 ml/hour) (Group C), respectively. The occurrence of CIN was evaluated based on serum Cr and GFR in three studied groups, before and after angiography procedure. The analysis of variance and paired t-test were used for data analysis by SPSS.

RESULTS: The serum Cr increased and GFR decreased significantly during the intervention in three groups ($P < 0.010$). However, the amounts of these changes were equal between groups ($P > 0.050$).

CONCLUSION: The study showed that nor the addition of NAC neither the addition of AA to sodium chloride infusion has more beneficial effect than hydration with sodium chloride, in the prevention of CIN.

Keywords: Contrast Media, N-Acetylcysteine, Ascorbic Acid, Sodium Chloride Solution

Date of submission: 19 Jan 2014, ***Date of acceptance:*** 27 Jun 2015

Introduction

In accordance with increasing cardiovascular disease and development of effective diagnostic and interventional procedures, the rate of their related complications such as contrast induced nephropathy (CIN) has been increased.[1,2] CIN is defined as serum creatinine (Cr) rising in patients using intravenous contrast for diagnostic or therapeutic procedure.[3] The incidence rate of CIN in the general population has reported about 2%, but is higher in high-risk population with estimate rate of 12-50%.[4] Though CIN has a benign course and in almost all of the cases its related renal impairment is transient but it considered as the third leading cause of acute renal failure in hospitalized patients and is associated with increased risk of morbidity, mortality, and medical care costs.[5,6] The exact mechanism of CIN and its related renal impairment has not understood yet. Some evidences suggested that factors such as increasing level of adenosine, endothelin, and free radicals and decreasing level of prostaglandins and nitric oxide after using contrast media may result in renal hemodynamics impairment, renal tubular cells toxicity and consequently renal failure.[7-9] Several preventative strategies including using calcium-channel antagonists, atrial natriuretic peptide, adenosine antagonists, and dopamine have been investigated in this regard, and different controversial results have been reported.[10,11] Pre-procedural hydration like an infusion of sodium chloride or half saline, considered as one of the

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most effective strategies for prevention of CIN.[12] Moreover, regarding the fact that one of the reported factors in the pathogenesis of CIN are oxygen free radical, the concept of using antioxidant agents such as N-acetylcysteine (NAC) or ascorbic acid (AA) have been developed in the treatment of CIN. However, the effectiveness of mentioned antioxidants is controversial.[13,14] Previous studies demonstrated that combination therapy of NAC and AA had not any additive effect in preventing CIN probably due to their similar mechanism of oxygen free radical scavenging.[15]

The role of normal saline (NS) is evaluated in several studies and mentioned as a standard strategy for prevention of CIN. Additional drugs were added to NS for increasing effect of prevention strategy; however, results of these studies are different and controversial, so it seems that additional investigations are needed for detection of the best preventive method. Therefore, the aim of this study was the evaluation and comparison of the effects of two antioxidant agents, including NAC and AA plus NS with the traditional approach (NS) in preventing of CIN in the patients undergone coronary angiography.

Materials and Methods

In a randomized clinical trial, 120 patients who scheduled for elective coronary angiography were enrolled. This study was done in Hajar Hospital, Shahrekord, Iran. The study protocol was approved by Regional Bioethics Committee of Shahrekord University of Medical Sciences (Research project number; 934). Iranian registration clinical trial (IRCT) number is "IRCT 2015050722134N1." Written informed consent was obtained from all selected patients. We prospectively selected 120 patients with baseline Cr level of > 1.5 mg/dl or glomerular filtration rate (GFR) ≤ 60. Patients with oliguria (< 400 cc/24 hours), severe heart failure with left ventricular ejection fraction < 35%, contrast-agent hypersensitivity, pregnancy, lactation, acute renal failure, IV use of contrast medium within previous week, vitamin C supplements use within previous week were excluded. Selected patients were allocated in three treatment groups randomly to receive oral NAC plus NS, (Group A), oral ascorbic acid plus NS (Group B) and intravenous NS (Group C). Patients of Group A received NAC (600 mg) bid (from 24 hours before to 24 hours after the procedure) plus NS (100 ml/hour from 12 hours before to 12 hours after the procedure). For Group B patients AA 500 mg (250 mg 12 hours before and 12 hours after the procedure) plus NS (100 ml/hour, 12 hours before to 12 hours after the procedure) prescribed. Group C patients received only NS (100 ml/hour, 12 hours before to 12 hours after the procedure). The occurrence of CIN and mean of Cr and GFR in three studied groups, before and 72 hours after the procedure was evaluated and compared.

CIN defined as increase ≥ 0.5 mg/dl in serum Cr or decrease ≥ 25% of GFR after 72 hours. Serum Cr was measured using Pars Azmoon Diagnostic Kits (Tehran-Iran) by BT 3000 equipment. GFR was measured using the Cockcroft-Gault equation [(140-age) × Body Weight/72 × Cr].[16]

Data were shown as means ± standard deviation. Because the sample size was moderately high in each group, so the parametric analysis of variance (ANOVA) was used to comparing the variables between groups. Paired t-test was used for comparing the change of variables during the study. Statistical analysis was done by SPSS software (version 17, SPSS Inc., Chicago, IL, USA) and $P < 0.050$ were determined as statistically significant.

Results

In this clinical trial 120 patients, including 80 (66.7%) male and 40 (33.3%) female were randomly entered in three groups, each one including 40 patients. There were 26, 27, and 26 males in the Group A (oral NAC plus NS), Group B (oral AA plus NS) and Group C (intravenous NS) respectively. The chi-square test did not show any significant difference between the distribution of sex in the groups ($P = 0.313$). The overall age of patients was from 38 to 81 years with the mean of 67.6 ± 8.1 years. The mean age of patients in the Groups of A, B, and C was 67.5 ± 7.5, 67.8 ± 6.8 and 67.6 ± 8.1 years respectively. The ANOVA test did not show any significant difference between the age of patients in the three groups ($P = 0.127$).

The results of serum Cr and GFR in the three groups before and after the study was shown in table 1. The amount of serum Cr ($P = 0.661$) and GFR ($P = 0.785$) were equal in the three groups of patients at the beginning of the study. The serum Cr increased, and GFR decreased significantly during the intervention in three groups (Table 1). However, the amounts of these changes were equal between groups (Table 1).

Table 1. Comparison the mean of serum creatinine (Cr) and glomerular filtration rate (GFR) in the three groups before and after the study

	Group A (n = 40)	Group B (n = 40)	Group C (n = 40)	P*
Cr				
Before intervention	1.68 ± 0.28	1.61 ± 0.36	1.66 ± 0.35	0.661
After intervention	1.74 ± 0.37	1.69 ± 0.34	1.75 ± 0.36	0.771
Change	0.06 ± 0.12	0.08 ± 0.14	0.09 ± 0.13	0.716
P** (before-after)	0.002	0.001	0.001	-
GFR				
Before intervention	54.80 ± 7.00	55.70 ± 6.00	55.30 ± 5.60	0.785
After intervention	53.60 ± 7.50	52.90 ± 5.70	52.90 ± 6.70	0.876
Change	-1.22 ± 2.42	-2.75 ± 2.83	-2.45 ± 2.83	0.074
P** (before-after)	0.003	0.001	0.001	-

* Based on ANOVA test; ** Based on paired t-test; Cr: Creatinine; GFR: Glomerular filtration rate; ANOVA: Analysis of variance

Discussion

This study showed that adding of NAC and AA have not any significant superior effect than traditionally used NS for preventing of CIN. Though several studies performed in this field, but differences in study designs such as patient selection, protocol of prophylaxis including dose of drugs and its administration form make the determination of an optimal approach for the prevention of CIN as a challenging issue in this field. In this study, the outcome of all three administrated regimens was similar. NAC and AA as antioxidant agents have not more advantages than sodium chloride in preventing CIN. The nephroprotective effect of NAC has been reported in many studies.[17,18] Accordingly the mentioned protective effect of NAC is mostly reported in patients with higher risk of nephropathy.[19] However, there are controversies regarding the effectiveness of NAC in reducing the occurrence of CIN in its different doses and type of administration. There were also studies which failed to confirm the protective effect of NAC in CIN.[20,21] The influence of orally administrated NAC (600 mg/twice daily) for CIN prevention first time was investigated by Tepel et al.[22] They reported that administration of oral NAC plus hydration was more effective than hydration alone for prevention CIN in patients with chronic renal failure using a low-osmolality contrast agent. A.C.T investigators[23] in their recent meta-analysis have announced that reports regarding the effectiveness of NAC belong to smaller clinical trials with an inappropriate methodology which tended to overestimate the role of NAC in this regard. Similar our results, Ozcan et al. have indicated that oral NAC plus hydration therapy have not any additional effect than hydration with sodium chloride alone.[24]

The efficacy of AA for prevention of CIN, have been studied both in animal and human studies, for example Spargias et al.[14] have studied the effect of high dose of AA, in 231 patients with a serum Cr ≥ 1.2 mg/dl. The mean increase in serum Cr level was significantly higher in the placebo group than AA group. They concluded that prophylactic orally administrated AA may have a protective effect for CIN in high-risk patients undergoing the coronary procedure. Similarly, in a recent study in Slovenia, Dvorsak et al.[25] reported that AA could have a protective role for CIN in patients with mild renal function impairment not in those with chronic renal failure.

Some similar studies have evaluated the effectiveness of our studied agents (NAC and AA) in preventing CIN among patients undergone coronary angiography, and different results have reported in this regard. Brueck et al.[26] in a prospective randomized double-blind placebo controlled trial have investigated the effect of NAC (600 mg, IV) or AA (500 mg, IV) versus placebo to prevent contrast-induced acute kidney injury in chronic kidney disease patients (serum Cr ≥ 1.3) undergoing elective cardiac catheterization. They concluded that standard doses of NAC and AA did not prevent CIN in the high-risk patients with non-ionic, low-osmolality contrast agent. Briguori et al.[27] in the North American synchrophasor initiative (NASPI) study, found that NAC was more effective than AA in CIN prevention, however, the current study did not find the same results. As mentioned above there are controversy in the results of studies because the different protocol of prevention, the dose of drugs, studied population and type of drug administration. It seems that prophylactic effect of AA is higher in patients with renal insufficiency than normal renal function. Regarding the inappropriate

preventative effect of AA, factors such as its dose which was lower than previous studies or the administration form (oral) may explain the controversy in findings. Regarding the amount of administrated contrast media, as our study was single center and there were not any cases with repeated contrast media administration, so the effect of the amount of contrast agent was similar in all studied groups. In this study, we represented a single-center experience among a small sample size of patients, which considered the limitation of this study.

Conclusion

The current study showed that adding of NAC or AA to NS infusion had not more beneficial effect. Further studies are warranted to evaluate the optimal pre-procedural volume repletion or appropriate dose of preventative NAC and AA. In addition, it is recommended to use more accurate laboratory methods such as neutrophil gelatinase-associated lipocalin or cystatin C in addition to serum Cr for early detection of CIN.

Acknowledgments

We acknowledge all staff of Hajar Angiography and CCU Centers for their cooperation in this study.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Khaledifar A, Momeni A, Ebrahimi A, Kheiri S, Mokhtari A. **Comparison of N-acetylcysteine, ascorbic acid, and normal saline effect in prevention of contrast-induced nephropathy.** ARYA Atheroscler 2015; 11(4): 228-32.

Trends of 28 days case fatality rate after first acute myocardial infarction in Isfahan, Iran, from 2000 to 2009

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Original Article

Abstract

BACKGROUND: The purpose of the present study was the analysis of the trends in case fatality rate of acute myocardial infarction (AMI) in Isfahan, Iran. This analysis was performed based on gender, age groups, and type of AMI according to the International Classification of Diseases, version 10, during 2000-2009.

METHODS: Disregarding the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA), this cohort study considered all AMI events registered between 2000 and 2009 in 13 hospitals in Isfahan. All patients were followed for 28 days. In order to assess the case fatality rate, the Kaplan-Meier analysis, and to compare survival rate, log-rank test were used. Using the Cox regression model, 28 days case fatality hazard ratio (HR) was calculated.

RESULTS: In total, 12,900 patients with first AMI were entered into the study. Among them, 9307 (72.10%) were men and 3593 (27.90%) women. The mean age in all patients increased from 61.36 ± 12.19 in 2000-2001 to 62.15 ± 12.74 in 2008-2009, (P = 0.0070); in women, from 65.38 ± 10.95 to 67.15 ± 11.72 (P = 0.0200), and in men, from 59.75 ± 12.29 to 59.84 ± 12.54 (P = 0.0170),. In addition, the 28 days case fatality rate in 2000-2009 had a steady descending trend. Thus, it decreased from 11.20% in 2000-2001 to 07.90% in 2008-2009; in men, from 09.20% to 06.70%, and in women, from 16.10% to 10.90%. During the study, HR of case fatality rate in 2000-2001 declined; therefore, in 2002-2003, it was 0.93 [95% confidence interval (CI) = 0.77-1.11], in 2004-2005, 0.88 (95% CI = 0.73-1.04), in 2006-2007, 0.67 (95% CI = 0.56-0.82), and in 2008-2009, 0.69 (95% CI = 0.56-0.82).

CONCLUSION: In Isfahan, a reduction was observable in the trend of case fatality rate in both genders and all age groups. Thus, there was a 29.46% reduction in case fatality rate (27.17% in men, 32.29% in women) during the study period.

Keywords: Case Fatality Rate, Myocardial Infarction, Trend, Iran

Date of submission: 30 Jul 2014, ***Date of acceptance:*** 2 May 2015

Introduction

Coronary heart disease (CHD) remains one of the leading causes of death in both genders in developed countries.[1] The incidence of mortality due to cardiovascular disease has been diminishing over the previous 3 decades in many developed countries.[2] Reduced incidences, promotion of secondary prevention measures, use of new treatments during

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the acute phase, and improved survival after myocardial infarction (MI) have contributed to the declining mortality rates.[3-5] However, MI is a primary cause of mortality and disability in the Iranian population.[6] Age, sex, cardiovascular risk factors, coronary history, acute MI (AMI) location, complications, treatments received during hospitalization and after hospital discharge, and the type of hospital are among the variables that may influence early or late mortality following an AMI.[7-10]

Most of the centers showed a decline in short-term case fatality rate, but the Isfahan center, Iran, did not.[5] The purpose of the present study was the analysis of the trends of case fatality rate of AMI in Isfahan and Najafabad based on gender, age groups, and type of AMI in patients treated during 2000-2009. Type of AMI was determined according to the International Classification of Disease, version 10 (ICD10) and using streptokinase.

Materials and Methods

Isfahan is a city in the center of Iran, an Eastern Mediterranean country, and is the second largest city of Iran. Previous studies have shown a relatively high rate of cardiovascular risk factors in this industrial city.[11-15]

During the study period, about 13 hospitals were admitting and managing patients with CHD in Isfahan. More than 75% of patients who had experienced MI were managed in 4 public hospitals and the rest in the remaining 9 private hospitals. Except for military hospitals, which did not allow access to their patients' records, other hospital records were evaluated. Among these hospitals, 4 were private and 9 public or university hospitals.[16]

In this registry, all possible CHD events were registered disregarding the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) age limitation. In this study, the MONICA definition (non-fatal definite events and fatal definite or possible events) is used for MI events. Moreover, only first events and patients classified as one group according ICD10 are included.

The research team involved in the program consisted of cardiologists and general practitioners, a number of nurses trained in receiving and recording patients' information, and professional biostatistician and epidemiologist. Identification and separation of patients with AMI based on ICD10 was performed by a cardiologist. Hospital discharge lists were used for case finding. Records of patients hospitalized in cardiology wards, coronary care units, or other wards but under the complete or partial supervision of cardiologists, were evaluated for possible signs and symptoms of CHD events. Basic information related to patients were collected by trained nurses, who used special forms to interview patients or obtained information from their hospital records. Symptoms and cardiac enzymes codes were classified in a manner similar to the MONICA project.[17] They summarized accurate records in special checklists containing information on age, sex, event and hospitalization dates, symptoms, history of previous MI, enzymes, admission electrocardiogram, whether the event was iatrogenic, survival status at discharge and after 28 days follow-up, and whether thrombolytic therapy was used during hospitalization. An expert nurse with special training in the MONICA registration system checked the filled records. Moreover, 10% of the checklists were randomly chosen and refilled by the expert nurse using the original hospital records and compared with those completed by registered nurses to see if any mistakes occurred. Then, data was collected from the Isfahan Cardiovascular Research Center (ICRC). As the center of Isfahan Province, MI patients who live in other cities of the province are also admitted to these hospitals. In order to calculate MI survival rate in Isfahan, only records from Isfahan and Najafabad city inhabitants were included in the study.[16]

A period of 28 days was used to define the case-fatality rate and to distinguish between events.[18] All discharged MI patients were followed using telephone calls, and if not available, reached through their address. The patients or close family members were asked about patients' health status. If a patient had died during the first 28 days after the event, death scenario was asked.[16] Detailed descriptions of the methods used in this project have been provided in previous reports.[16,19-24]

Overall, 14,450 patients (10,334 men and 4116 women) with first AMI, who were inhabitants of Isfahan and Najafabad were entered into the study. Subsequently, 886 patients (564 men and 322 women) were excluded because their AMI type was not determined according to the ICD10. Furthermore, 118 patients (82 men and 36 women) were exclude from the study, because they died during the 28 days after the first attack without any sign of cardiovascular disease and due to accident, suicide, homicide, chronic obstructive pulmonary disease, cancer, liver cirrhosis, rheumatic heart disease, vascular disease, or atherosclerosis. In addition, 418 patients (292 men and 126 women) were excluded because outcome was unknown. Moreover, 128 patients (89 men and 39 women)

were excluded from the study, because the exact date of occurrence or death from the disease was not specified and the 28 days duration after the attack could not be calculated in these cases.[17] Therefore, 12,900 patients, 9307 (72.15%) men and 3593 (27.85%) women, remained in the study.

The study period, from 2000 to 2009, was divided into 5 2-year periods (2000-2001, 2002-2003, 2004-2005, 2006-2007, and 2008-2009). Case fatality rates were adjusted for age through direct standardization. Standardization was based on 4 age groups; ≤ 40, 41-60, 61-80, and ≥ 81 years. In order to compare age average in the study, t-test and analysis of variance (ANOVA) were used. To assess the case fatality rate according to each period, Kaplan-Meier analysis, and to compare case fatality rate, log-rank test were used. Short-term (28 days) case fatality hazard ratio (HR) was calculated using the Cox regression model for every 2-year period. The first period (2000-2001) was considered as reference, and other periods were compared with this group and 95% confidence interval (CI) was calculated. The trend of streptokinase use in the treatment of AMI in hospitals was evaluated in every 2-year period. SPSS software (version 15, SPSS Inc., Chicago, IL, USA) was used for data analysis. The significance value was set to $P < 0.050$.

Results

In total, this study included 12,900 fatal and non-fatal first AMI events, of which 9307 (72.15%) were men and 3593 (27.85%) women. Sex ratio (male/female) was 2.59. Patient's demographic and clinical data is presented in table 1. The distribution of first AMI and 28 days case fatality rate in 10 years (for every 2 years separately) of the study periods is shown in table 2. Of the 12,900 patients with AMI entered into the study, 1198 died during the 28 days after their MI event (overall case fatality rate = 09.30% and survival rate = 90.70%). Of the 9307 men, 697 died (case fatality rate = 07.50% and survival rate = 92.50%) and of the 3593 women, 501 died (case fatality rate = 13.90% and survival rate = 86.10%) ($P < 0.001$).

A steady descending trend was observed in the 28 days case fatality rate during the study period (2000-2009); it decreases from 11.82% in 2000-2001 to 07.90% in 2008-2009. In fact, we observed a 03.92% decrease in case fatality rate from 2000-2001 to 2008-2009, and 29.46% improvement in survival rate compared to 2000-2001. However, this trend has been in both genders. Therefore, in men, it decreased from 09.20% in 2000-2001 to 06.70% in 2008-2009 (meaning a 02.5% decrease in case fatality rate from 2000-2001 to 2008-2009 and 27.17% improvement in survival rate compared to 2000-2001). In women, it decreased from 16.10% in 2000-2001 to 10.90% in 2008-2009 (meaning a 05.20% decrease in case fatality rate from 2000-2001 to 2008-2009 and 36.80% improvement in survival rate compared to 2000-2001) (Table 2 and Figure 1).

However, this trend was observed in HR of 28 days case fatality rate from AMI during the study period. Thus, in comparison with 2000-2001, in 2002-2003, 2004-2005, 2006-2007, and 2008-2009, HR was 0.93 (CI 95% = 0.77-1.11), 0.88 (CI 95% = 0.73-1.04), 0.67 (CI 95% = 0.56-0.82), and 0.69 (CI 95% = 0.56-0.82), respectively. This trend was observable in both genders. In men, HR, respectively, was 0.98 (CI 95% = 0.74-1.30), 0.95 (CI 95% = 0.75-1.29), 0.73 (CI 95% = 0.54-0.98), and 0.67 (CI 95% = 0.49-0.91). In women, it was 0.91 (CI 95% = 0.72-1.15), 0.8 (CI 95% = 0.64-1.00), 0.66 (CI 95% = 0.51-0.84), and 0.71 (CI 95% = 0.56-0.92), respectively (Table 2).

Mean age of all patients was 61.80 ± 12.60; in men it was 60.00 ± 12.50 and in women 66.72 ± 11.34. This difference was statically significant ($P \leq 0.0010$). To examine changes in age of disease occurrence over time, the study period was divided into 5 2-year periods. Mean age of all patients increased from 61.36 ± 12.19 in the primary period (2000-2001) to 62.61 ± 12.81 in the final period (2008-2009). This difference was statically significant ($P = 0.0070$). There was a raising trend in mean age in men and women in the study period. For women, in the primary period, it was 65.38 ± 10.95 and in the final period was 67.15 ± 11.72 ($P = 0.0200$). For men, in the primary period, it was 59.75 ± 12.29 and in the final period 59.84 ± 12.54 ($P = 0.0170$) (Table 3). In addition, this trend was observed in mean age at time of death. Thus, in the primary period, it was 68.00 ± 10.60 and in the final period, 71.40 ± 9.53 ($P = 0.0200$). This trend was observed in men and women, but it was only significant in women. For women, in the primary period, it was 68.86 ± 10.41 and in the final period, 73.11 ± 08.94 ($P = 0.0440$). For men, in the primary period, it was 67.40 ± 10.73, and in the final period, 70.31 ± 08.70 ($P = 0.1640$) (Table 3).

Table 4 shows the trends of case fatality rate for each age group. Case fatality rate decreased in a steady pattern in all age groups with the increase in age. Consequently, there was a 60, 60, 19.31, and 46.75 percent reduction in case fatality rate in the final period (2008-2009), compared to the primary

period (2000-2001), respectively, for < 40, 41-60, 61-80, and > 81 age groups (Table 4).

In this study, based on ICD10, AMI was classified into 6 groups; acute transmural MI of anterior wall, acute transmural MI of inferior wall, acute transmural MI of other site, acute transmural MI of unspecified site, acute sub endocardial MI and AMI, and unspecified. Because the number of patients in acute transmural MI of other sites and acute transmural MI of unspecified site was small and very unstable, we considered these two groups as one group. In Isfahan and Najafabad, based ICD10, from 2000 to 2009 no evident trend was observed in 10 years case fatality rate. However, difference in average case fatality rate between types of AMI, according to ICD10, was statistically significant (P < 0.0001) (Table 5).

In addition, use of streptokinase in the treatment service during the study period had no clear trend. In average, 51.8% (minimum of 48.3% and maximum of 56.40%) of patients received streptokinase, 55.70% in men (minimum of 52.20% and maximum of 61.80%) and 41.70% in women (minimum of 38.20% and maximum of 44.70%). Furthermore, 48.20% (minimum of 43.60% and maximum of 51.70%) of patients did not receive streptokinase; 47.80% in men (minimum of 38.20% and maximum of 47.80%) and 61.80% in women (minimum of 55.30% and maximum of 61.80%) (Table 6).

Table 1. Demographic and clinical data of hospitalized myocardial infarction (MI) patients in Isfahan

Variables	Men			Women			Total		
	Live	Death	Total	Live	Death	Total	Live	Death	Total
Age in men									
39 year and lower	427	98	525	336	114	450	763	212	975
40-49	394	5	399	42	2	44	436	7	443
50-59	1587	42	1629	225	11	236	1812	53	1865
60-69	2423	102	2525	579	48	627	3002	150	3152
70-79	2150	193	2343	933	123	1056	3083	316	3399
80 year and older	1629	257	1886	977	203	1180	2606	460	3066
Streptokinase									
Receiving	4864	317	5181	1269	229	1498	6133	546	6679
Not receiving	3746	380	4126	1823	272	2095	5569	652	6221
ICD, version 10									
Acute sub endocardial MI	2979	213	3192	950	126	1076	3929	339	4268
Acute transmural MI of other sites	2650	109	2759	825	86	911	3475	195	3670
Acute transmural MI of inferior wall	225	7	232	84	11	95	309	18	327
Acute transmural MI of anterior wall	82	24	106	28	25	53	110	49	159
AMI, unspecified	736	16	752	446	20	466	1182	36	1218
Acute transmural MI of unspecified site	1938	328	2266	759	233	992	2697	561	3258
The first center was referred									
Non-specialized hospitals	573	65	638	185	53	238	758	118	876
Specialized hospital	7547	590	8137	2747	418	3165	10294	1008	11302
Unknown	208	27	235	66	14	80	274	41	315
Health networker clinic	282	15	297	94	16	110	376	31	407
Symptoms									
Typical	7250	523	7773	2518	380	2898	9768	903	10671
A typical	993	92	1085	376	48	424	1369	140	1509
Others	339	75	414	183	69	252	522	144	666
Miss	28	7	35	15	4	19	43	11	54
Cardiac enzymes									
A typical	1026	61	1087	509	66	575	1535	127	1662
Typical	6597	483	7080	2196	306	2502	8793	789	9582
Others	780	45	825	291	43	334	1071	88	1159
Not clear	207	108	315	96	86	182	303	194	497
Hospital									
Academic hospitals	7894	650	8544	2842	465	3307	10736	1115	11851
Privative hospitals	716	47	763	250	36	286	966	83	1049

ICD: International Classification of Diseases; Cardiac enzymes: Lactate dehydrogenase, creatine kinase, and Troponin

Table 2. Trend of case fatality rate of acute myocardial infarction (AMI) according to gender in Isfahan and Najafabad from 2000 to 2009

Years	Total (n)	Number of events	Case fatality rate	HR of case fatality (95% CI)
Men				
Overall	9307	697	7.5	-
2000-2001	1331	123	9.2	R
2002-2003	1877	159	8.5	0.98 (0.74-1.30)
2004-2005	2208	166	7.5	0.98 (0.75-1.29)
2006-2007	2029	125	6.2	0.73 (0.54-0.98)
2008-2009	1862	124	6.7	0.67 (0.49-0.91)
Women				
Overall	3593	501	13.9	-
2000-2001	533	86	16.1	R
2002-2003	719	112	15.6	0.91 (0.72-1.15)
2004-2005	893	139	15.6	0.81 (0.64-1.00)
2006-2007	725	85	11.7	0.66 (0.51-0.84)
2008-2009	723	79	10.9	0.71 (0.56-0.92)
Total				
Overall	12900	1198	09.3	-
2000-2001	1864	209	11.2	R
2002-2003	2596	271	10.4	0.93 (0.77-1.11)
2004-2005	3101	305	09.8	0.88 (0.73-1.04)
2006-2007	2754	210	07.6	0.67 (0.56-0.82)
2008-2009	2585	203	07.9	0.69 (0.57-0.84)

R: Reference group; HR: Hazard ratio; CI: Confidence interval

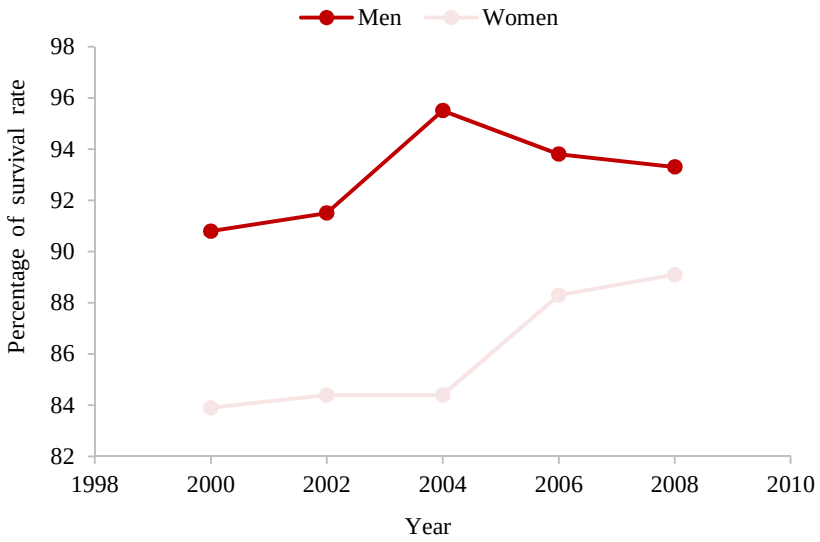

Figure 1. Trend of survival rate of acute myocardial infarction according to gender in Isfahan and Najafabad from 2000 to 2009

Table 3. Trend of change in mean age of patients with acute myocardial infarction (AMI) at time of occurrence and death in Isfahan and Najafabad from 2000 to 2009

Years	Number of men	Mean age in men	P	Number of women	Mean age in women	P	Number of patients	Mean age in patients	P	Sex ratio (men/women)
Age of disease occurrence										
Overall	9307	60.00 ± 12.54		3593	66.77 ± 11.37		12900	61.90 ± 12.60		2.59
2000-2001	1331	59.75 ± 12.29		533	65.38 ± 10.95		1864	61.36 ± 12.19		2.49
2002-2003	1877	59.77 ± 12.44	0.017	719	66.89 ± 11.14	0.020	2596	61.74 ± 12.51	0.007	2.61
2004-2005	2208	59.60 ± 12.59		893	66.62 ± 11.45		3101	61.62 ± 12.68		2.47
2006-2007	2029	60.13 ± 12.50		725	67.46 ± 11.34		2754	62.06 ± 12.63		2.79
2008-2009	1862	59.84 ± 12.54		723	67.15 ± 11.72		2585	62.61 ± 12.81		2.57
Age in death time										
Overall	697	68.12 ± 11.15		501	71.46 ± 10.27		1198	69.52 ± 10.91		1.40
2000-2001	123	67.40 ± 10.73		86	68.86 ± 10.41		209	68.00 ± 10.60		1.43
2002-2003	159	67.16 ± 11.30	0.164	112	71.27 ± 10.58	0.044	271	68.86 ± 11.17	0.020	1.41
2004-2005	166	67.94 ± 11.20		139	71.40 ± 10.52		305	69.51 ± 11.00		1.19
2006-2007	125	68.13 ± 12.40		85	72.90 ± 10.12		210	70.06 ± 11.74		1.47
2008-2009	124	70.31 ± 8.70		79	73.11 ± 08.94		203	71.40 ± 09.53		1.56

Table 4. Trend of case fatality rate of acute myocardial infarction (AMI) according to age groups in Isfahan and Najafabad from 2000 to 2009

Age group	< 40			41-60			61-80			> 81		
(year)	Patients	Death	Case fatality rate (%)	Patients	Death	Case fatality rate (%)	Patients	Death	Case fatality rate (%)	Patients	Death	Case fatality rate (%)
Overall	556	11	1.97	5323	225	4.2	6285	804	12.8	736	159	21.6
2000-2001	87	2	2.30	734	47	6.4	985	143	14.5	58	17	29.3
2002-2003	119	4	3.40	1048	56	5.3	1309	175	13.4	120	36	30.0
2004-2005	146	1	0.70	1333	59	4.4	1456	205	14.1	166	40	24.1
2006-2007	96	3	3.10	1163	36	3.1	1315	138	10.5	180	33	18.3
2008-2009	108	1	0.90	1045	26	2.5	1220	143	11.7	212	33	15.6

Table 5. Trend of case fatality rate of acute myocardial infarction (AMI) according to type of AMI based on the International Classification of Diseases 10 (ICD10) in Isfahan and Najafabad from 2000 to 2009

AMI based ICD10	Acute transmural MI of anterior wall		Acute transmural MI of inferior wall		Acute transmural MI of other sites and acute transmural MI of unspecified site		Acute subendocardial MI		unspecified AMI		Total	
	Total N (Death N)	Case fatality rate (%)	Total N (Death N)	Case fatality rate (%)	Total N (Death N)	Case fatality rate (%)	Total N (Death N)	Case fatality rate (%)	Total N (Death N)	Case fatality rate (%)	Total N (Death N)	Case fatality rate (%)
Overall	4268 (339)	9.1	3670 (195)	5.3	486 (67)	13.8	1218 (36)	3.0	3258 (561)	17.2	12900 (1198)	09.3
2000-2001	74 (69)	9.5	602 (40)	6.6	192 (46)	24.0	200 (10)	5.0	145 (44)	30.3	1864 (209)	11.2
2002-2003	94 (98)	9.9	836 (60)	7.2	90 (8)	08.9	260 (6)	2.3	416 (99)	23.8	2596 (271)	10.4
2004-2005	996 (75)	5.0	888 (44)	5.0	102 (6)	05.9	269 (2)	0.7	846 (178)	21.0	3101 (305)	09.8
2006-2007	762 (40)	5.2	707 (30)	4.2	74 (5)	06.8	265 (7)	2.6	946 (128)	13.5	2754 (210)	07.6
2008-2009	791 (57)	7.2	637 (21)	3.3	28 (2)	07.1	24 (11)	4.9	905 (112)	12.4	2585 (203)	07.9

AMI: Acute myocardial infarction; MI: Myocardial infarction; ICD10: International Classification of Diseases 10

Table 6. Trend of use of streptokinase in treatment of acute myocardial infarction (AMI) according to gender in Isfahan and Najafabad from 2000 to 2009

Streptokinase	Men			Women			Total		
	Receiving streptokinase [n (%)]	Not receiving streptokinase [n (%)]	Streptokinase total [n (%)]	Receiving streptokinase [n (%)]	Not receiving streptokinase [n (%)]	Streptokinase total [n (%)]	Receiving streptokinase [n (%)]	Not receiving streptokinase [n (%)]	Streptokinase total [n (%)]
Overall	5181 (55.7)	4126 (47.8)	9307 (100)	1498 (41.7)	2095 (58.3)	3593 (100)	6679 (51.8)	6221 (48.2)	12900 (100)
2000-2001	823 (61.8)	508 (38.2)	1331 (100)	229 (43.0)	304 (57.0)	533 (100)	1052 (56.4)	812 (43.6)	1864 (100)
2002-2003	1022 (54.4)	855 (45.6)	1877 (100)	291 (40.5)	428 (59.5)	719 (100)	1313 (50.6)	1283 (49.4)	2596 (100)
2004-2005	1267 (57.4)	941 (42.6)	2208 (100)	399 (44.7)	494 (55.3)	893 (100)	1666 (53.7)	1435 (47.3)	3101 (100)
2006-2007	1097 (54.1)	932 (45.9)	2029 (100)	303 (41.8)	422 (58.2)	725 (100)	1400 (50.8)	1354 (49.2)	2754 (100)
2008-2009	972 (52.2)	890 (47.8)	1862 (100)	276 (38.2)	447 (61.8)	723 (100)	1248 (48.3)	1337 (51.7)	2585 (100)

Discussion

In the present study, we have demonstrated a consistent decrease in case fatality rate following a first MI in Isfahan, during a 10 years period from 2000 to 2009. The decreasing trend of case fatality rate was observable in both genders and all age groups. There was a 29.46% reduction in case fatality rate in the final period (2008-2009) compared with the primary period (2000-2001). A 27.17% decrease was observed in men, and 32.29% in women. Moreover, a 60% decrease in the ≤ 40 age group, 60% in 41-60 age group, 19.31% in 61-80, and 46.75% in ≥ 80 was observed. In addition, in the duration of the study, there was a decreasing trend in the HR of 28 days case fatality rate in all patients.

In this study, the majority of patients were men (72.10% men and 27.90% women) and women were older (66.77 ± 11.37 vs. 60.00 ± 12.54 years; P < 0.0010). The 28 days case fatality rate was higher in women than men (13.90 vs. 07.50%; < 0.0001). In a study conducted by Carine Milcent et al. in the French Hospitals Database, most patients were men (70% men and 30% women) and women were older (75 vs. 63 years of age; P < 0.0010) and had a higher rate of hospital mortality (14.80 vs. 06.10%; P < 0.0001) than men.[25] This was in agreement with the findings of the current study. However, the present analysis confirms the higher 28 days case fatality rate from AMI in women; the so-called "gender gap" reported in other studies.[26-29] In previous studies, we observed that crude hospital mortality rates for AMI in women was higher than men. This difference may be partly due to the higher average age of women at the time of disease occurrence and higher prevalence of comorbidities in women compared with men.[26] More frequent use of revascularization procedures in men may also account for the fewer deaths. Indeed, men with AMI tend to undergo more aggressive hospital treatments than women.[30,31] We observed a similar result in the Iranian treatment system; during the study, an average higher proportion of men received streptokinase than women (55.70% men and 41.70% women). However, the impact of lower rates of revascularization is controversial. In some studies, older age and higher baseline risk are presented as the causes of higher rates of mortality in women.[32,33] In addition, some studies inferred that treatment in women had no effect on short-term survival from AMI.[27,34] Case fatality rate of AMI in 2008-2009 was 29.46% less than in 2000-2001 (in men 27.17% and in women 32.29%), which coincides with the results of other hospital registered studies.[35-37] HR of 28 days case fatality rate of AMI in 2008-2009 was 0.69 (95% CI = 0.56-0.82) compared with 2000-2001; for men and women, it was 0.63 (95% CI = 0.45-0.88) and 0.70 (95% CI = 0.54-0.90), respectively. A similar result was obtained in a European register on acute coronary syndrome, that compared 30 days mortality in 2000 and 2004 [odds ratio (OR) = 0.85 (0.73-0.99)].[38] In the study by MacIntyre et al., 28 days case fatality rate increased with increasing of age.[39] However, in this study, with the rising trend in mean age in the disease occurrence a steady decline was observed in case fatality rate. It is evident that the severity of infarctions decreased over time. A hypothesis is that the increasing use of medications such as aspirin and β-blockers before admission may reduce the size and severity of infarctions.[40] Therefore, over time this could be effective in reducing the AMI case fatality rate.

Population-based studies all documented a favorable decline in early mortality among younger individuals contrasting with a persistently high fatality rate among the elderly over a period of time ranging from 1975 to 1995.[2,41-44] More importantly, the mortality rate of infarction in the community remained high and was consistently higher than that reported in clinical trials, reflecting their inherent selection processes.[45] Although only clinical trials can test the efficacy of a new treatment, reports from community surveillance present important complementary insights into the effectiveness of care and treatments once implement. The current study demonstrates that the marked improvement in early fatalities after MI persisted over time and that notable survival gains were realized among the women and elderly, in whom discrepancy had been detected previously.[43] This article was conducted based on the MONICA project in Isfahan with the support and ethical approval of ICRC with the code 84130, in year 2012.

Limitations

A difficulty of this study is a lack of complete, community-based case ascertainment, which includes protocols for finding community fatal and non-fatal MI cases who are not admitted to hospitals. Most important limitation of the study is the lack of data about out-of-hospital fatal cases, such as MI cases managed at home or in health centers. This figure might be unimportant since MI event is considered an emergency in the Iranian health care system, and all hospitals should admit

such patients regardless of their insurance status. In the Danish MONICA population, this figure was measured to be > 01% of total MI cases in a year.[46] Therefore, omitting these patients will not lead to a sham decline in MI case fatality rates.

Conclusion

We have demonstrated a consistent decrease in case fatality rate following a first MI in Isfahan, during a 10-year period from 2000 to 2009. The decrease in the trend of case fatality rate in both genders and all age groups was observable. There was 29.46% reduction in case fatality rate in the final period (2008-2009) compared to the primary period (2000-2001); 27.17% in men and 32.29% in women. A 60%, 60%, 19.31%, and 46.75% reduction was observed in the ≤ 40 years, 41-60 years, 61-80 years, and ≥ 80 years age groups, respectively.

Acknowledgments

The authors would like to thank off all Isfahan Cardiovascular Research Institute Staff who helped in this study.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Mohammadian M, Hosseini Sh, Sadeghi M, Sarrafzadegan N, Salehiniya H, Roohafza H, et al. **Trends of 28 days case fatality rate after first acute myocardial infarction in Isfahan, Iran, from 2000 to 2009.** ARYA Atheroscler 2015; 11(4): 233-43.

Herbs with anti-lipid effects and their interactions with statins as a chemical anti- hyperlipidemia group drugs: A systematic review

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Review Article

Abstract

BACKGROUND: The present systematic review aimed to express the clinical anti-lipid effects of different types of herbs, as well as described studied interactions between herbal remedies and prescribed drugs for hyperlipidemic patients which were based on in vitro experiments, animal studies, and empirical clinical experiences.

METHODS: For this systematic review, we explored 2183 published papers about herbal drugs interactions from November 1967 to August 2014, fulfilling eligibility criteria by searching in some databases such as Web of Science, Medline, Scopus, Embase, Cinahl, and the Cochrane database. The main keywords used for searching included: herbal medicine, herbs, statin, lipid, and herb-drug interaction.

RESULTS: Among published articles about herb-drug interactions, 185 papers met the initial search criteria and among them, 92 papers were potentially retrievable including a description of 17 herbs and medicinal plants. In first step and by reviewing all published manuscripts on beneficial effects of herbs on serum lipids level, 17 herbs were described to be effective on lipid profile as lowering serum triglyceride, total cholesterol, low-density lipoprotein cholesterol as well as increasing serum high-density lipoprotein level. Some herbs such as celery could even affect the hepatic triglyceride concentrations. The herbal reaction toward different types of statins is varied so that grapefruit or pomegranate was interacted with only some types of statins, but not with all statin types. In this context, administration of herbal materials can lead to decreased absorption of statins or decreased the plasma concentration of these drugs.

CONCLUSION: Various types of herbs can potentially reduce serum lipid profile with the different pathways; however, the herb-drug interactions may decrease pharmacological therapeutic effects of anti-hyperlipidemic drugs that should be considered when approved herbs are prescribed.

Keywords: Herbal Medicine, Herbs, Statin, Lipid, Herb-Drug Interaction

Date of submission: 1 Mar 2015, ***Date of acceptance:*** 27 Jun 2015

Introduction

Ischemic heart disease is one of the major causes of mortality and disabilities whole of the world, particularly in developing countries. Because of its rapid progression in order to inappropriate lifestyle and nutritional modification, it has been produced as the greatest vulnerable event.[1] The pattern of the spread of disease is highly associated with quality control of its major risk factors that among them, hyperlipidemia has the main staple role.[2,3] Nowadays, tend to use synthetic drugs to lower serum lipid in patients with hyperlipidemia is gradually decreased because of their related side effects, as well as a progression of drug resistance. In this regard, tend to use of medicinal plants has been doubled.[4] However, in some cases, the multi-drug prescription such as using synthetic drugs and herbs become a necessary, leading herb-drug

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interaction that is a major concern of specialists in pharmacology. These interactions may also increase pharmacological therapeutic effect that is more important in drugs with low safety and narrow therapeutic indices.[5] Unfortunately, the vast majority of these products are used unlicensed without the assessment of efficacy, safety, or quality. Furthermore, some herbal supplements are frequently associated with adverse events including all levels of severity, organ systems, and age groups that may worsen drug interactions when used in conjunction with chemical drugs.[6] In addition, recent statistics have evidenced that as many as 16% of prescription drug users consume herbal supplements,[7] fewer than 40% of patients disclose their herbal supplement usage to health care providers,[8] and many physicians are unaware of the potential for herb-drug interactions.[9] This knowledge deficiency evidently increases the likelihood of drug-herb interactions. The present systematic review aimed to express the clinical anti-lipid effects of different types of herbs as well as described studied interactions between herbal remedies and prescribed drugs for hyperlipidemic patients which were based on in vitro experiments, animal studies, and empirical clinical experiences.

Materials and Methods

For this systematic review, we explored 2183 published papers about herbal drugs interactions from November 1967 to August 2014, fulfilling eligibility criteria by searching in some databases such as Web of Science, Medline, Scopus, Embase, Cinahl and the Cochrane database. Our research was restricted to English language studies. The main keywords used for searching included: herbal medicine, herbs, statin, lipid, and herb-drug interaction.

Studies were included, and eligible if evaluated herb-drug interactions in therapeutic regimens for treatment of hyperlipidemia. In this review, case reports were excluded.

Papers matching inclusion criteria were reviewed in detail. Methodology of papers quality assessment was performed on the basis of some methodological elements that were previously described.[10] These criteria were including: prospective data collection, method of sampling, age range specification, inclusion and exclusion items specification, study setting specification, measurement tools validation, definition of disease status, sex and age specific prevalence report, data collection description, study limitations and possible correlates of disease and complications.

Among 2183 published articles about herb-drug interactions, 185 papers met the initial search criteria and among them, 92 papers were potentially retrievable including a description of 17 herbs and medicinal plants.

Results

Anti-lipid effects of herbs and related mechanisms

Among all studies evaluating effects of herbs on lipid profile and also those who assessed interactions between these herbs and lipid-lowering drugs, especially statins (Table 1), a minority of the studies focused on herb-drug interactions. Furthermore, with respect to the mechanisms of action as well as biological pathways involving drug interactions, these mechanisms have not been completely understood. In some experimental studies, the main mechanisms involved in reducing lipid levels or its effects increase of lipid-resistance to lipid oxidation induced by some co-factors such as Cu(2+) (Basil or Ocimum basilicum).[11,12] Some herbal extracts acts as induced inhibition of lipid accumulation during adipogenesis particularly via improvement of triglyceride-rich lipoprotein catabolism (blueberry or Vaccinium myrtillus).[13,14] In some herbs, the main factors for the relevant bioactivity is enriched 9(Z)-octadecenamide (oleamide) and ethanolic extracts responsible for inhibition of lipid production leading lowering serum triglyceride, total cholesterol, low-density lipoprotein cholesterol (LDL-C) or even hepatic triglyceride (celery or Apium graveolens).[15-17] Some herbs such as dandelion (Taraxacum officinale) acts via inhibition of adipocyte differentiation and lipogenesis in 3T3-L1 preadipocytes resulted in potentially decrease in different lipid profile including triglycerides, total cholesterol and LDL-C, as well as increase of high-density lipoprotein cholesterol (HDL-C) level both within a mid-term administration time.[18-20] The ethanolic extract of some herbs such as Eugenol or Eugenia jambolana can improve 3-hydroxy-3-methylglutaryl-coenzyme A reductase activity that has a potential role in regulating serum lipid profile. It was also shown that hypolipidemic effect of this agent can be due to the presence of flavonoids, saponins, glycosides, and triterpenoids in its extract.[21-24] Modifying lipid peroxidation has been revealed as the main underlying mechanism of action in some herb extract (evening primrose oil) that is mediated by reduce of glutathione peroxidase activity and

increase of the activities of glutathione reductase and transferase.[25-30] In fenugreek (Trigonella foenum-graecum), the main mechanisms responsible for lowering serum triglyceride and total cholesterol include activating lecithin-cholesterol acyltransferase (47%), post heparin lipolytic activity (35%), triglyceride lipase (34%), lipoprotein lipase (20.8%), and increased excretion of fecal bile acids, as well as mediated through inhibition of fat accumulation and upregulation of LDL receptor (LDLR). In fact and at molecular level, thermostable extract of fenugreek seeds (TEFS) or TEFS can inhibit accumulation of fat in differentiating and differentiated 3T3-L1 cells through decreased expression of adipogenic factors such as peroxisome proliferators activated-receptor-gamma (PPAR-gamma), sterol regulatory element-binding protein-1, and CAAT element-binding proteins-alpha. Under sterol-enriched condition, TEFS up-regulated LDLR expression resulting in enhanced LDL uptake.[31-33] These underlying pathways are particularly revealed in diabetic states.[34-37] Ginger (Zingiber officinale) has been introduced as a lowering lipid peroxidation through its high acetylcholinesterase inhibitory activity. In fact, the inhibitory effect of ginger extracts on acetylcholinesterase activities and some prooxidants induced lipid peroxidation has been demonstrated that is usually mediated by effect on acetylcholinesterase activities, and sodium nitroprusside and quinolinic acid-induced lipid peroxidation.[38-42] Ginseng is a powerful herb affect via inhibition the increases of total cholesterol, LDL-C and triglyceride and also the decrease of HDL-C by down-regulating lipid accumulation and up-regulating adiponectin expression in the 3T3-L1 adipocyte cells. It seems that the main enzymatic pathways involved in this mechanisms include displaying 1,1-diphenyl-2-picrylhydrasyl and superoxide radical scavenging activities and inhibited hemolysis induced by 2,2'-azobis-2-amidinopropane dihydrochloride in a dose-dependent manner.[42-45] The anti-lipid effects of the grape are mostly mediated by resveratrol component that can significantly lower oxidized LDL and elevate HDL-C level that can be beneficial in atherosclerosis prevention. Moreover, administration of grape seed procyanidin extract (GSPE) can reverse the increase in plasma phospholipids. The alterations in the lipid metabolic pathways induced by GSPE were accompanied by lower free fatty acid levels in the plasma and decreased lipid and triglyceride accumulation. In this pathway, the effect of the oligomeric and polymeric procyanidin fractions in grape can also be trigger for lipolytic enzyme activities.[46-52] The strong effect of green tea polyphenols on reducing the body fat content and hepatic triacylglycerol and cholesterol accumulation has been also shown. It seems that green tea extract suppresses adiposity and affects the expression of lipid metabolism genes especially hepatic expression of the lipid catabolism genes acyl-coenzyme A oxidase 1, palmitoyl (ACOX1), acyl-coenzyme A dehydrogenase, c-4 to c-12 straight chain (ACADM), and peroxisome proliferator-activated receptor alpha (PPAR-α).[53-57] Analysis of methanolic extract and volatile oil extracted from Nigella sativa seed oil have shown reduction of the plasma triglycerides to near normal level and increase of HDL-C and its subfraction along with arylesterase activity levels caused by a significant decrease in hepatic hydroxymethylglutaryl (HMG)-CoA reductase activity.[58-63]

Table 1. Herbs with hypolipidemic effects

Name of herb	Biological effects
Basil	Lowering LDL and total cholesterol, increase of HDL
Blueberry	Lowering triglyceride and LDL levels
Celery	Decreasing serum triglyceride, total cholesterol, LDL-C and hepatic triglyceride
Dandelion	Decreasing serum triglyceride, total cholesterol, LDL-C and increasing HDL-C
Dill	Decreasing serum triglyceride
Eugenol	Decreasing serum triglyceride, total cholesterol, LDL-C and increasing HDL-C
Evening primrose oil	Decreasing serum triglyceride, total cholesterol
Fenugreek	Decreasing serum triglyceride, total cholesterol, HDL-C
Ginger	Decreasing serum LDL-C and increasing HDL-C
Ginseng	Decreasing serum triglyceride, total cholesterol, LDL-C and increasing HDL-C
Grape	Lowering oxidized LDL and elevate HDL-C level
Green tea	Suppresses adiposity and affects the expression of lipid metabolism genes
Nigella	Decrease in triglyceride and increase in HDL-C
Psyllium	Decrease in LDL

LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol

The beneficial effects of psyllium has been more focused on its regulatory effects on different components of metabolic syndrome such as improve glucose levels and insulin response, blood pressure, as well as lipid profile in both animals and humans, thereby reducing metabolic risk factors. According to recent reports, the use of psyllium could decrease insulin sensitivity, reduce android fat to gynoid fat ratio, as well as a reduce LDL-C. However, its physiological pathways have been already questioned.[64,65] Among different types of herbs, the position of dill as an anti-lipid agent is highlighted. Recent observations have been shown that the main hypolipidemic effect of this herb is order to activation of PPAR-α, an indispensable regulator for hepatic lipid metabolism by the extracts of dill caused by increased the mRNA expression levels of fatty acid oxidation-related genes in the liver and leading decrease of plasma triglyceride and glucose levels.[66] Its effect has been also shown in some recent clinical trials especially on lowering serum triglyceride level.[67]

Along with independent effects of the pointed herbs on lipid profile, some other herbal extracts such as red yeast rice or grapefruit indirectly influence serum lipid levels though their interactions with lipid-lowering drugs that are discussed in the next section.

Interaction between herbs and lipid lowering drugs

Regarding interaction between statin drugs and herbs which involved in lowering serum lipid profile, a few studies have been published. In a recent study by Rosenblat et al., although simvastatin with the dose 15 µg/ml could decrease macrophage cholesterol biosynthesis rate by 42% as compared to control cells, the combination of pomegranate and simvastatin resulted in an inhibitory effect up to 59% that was significant. Moreover, Simvastatin with the same dosage modestly decreased macrophage reactive oxygen species formation by 11% alone and by up to 63% concurrently with pomegranate.[68] In another experiment on interactive effects of grapefruit juice on chemical drugs, it has been revealed that the main mechanism for this interaction include inhibiting CYP3A4, the cytochrome P450 isoenzyme that most often involve in drug metabolism. With respect to interaction between grapefruit and statins, co-ingestion of this fruits can significantly elevated serum atorvastatin by 19-26% in one study and by 1.40 fold (95% confidence interval 1.02, 1.92) in another study compared with baseline and also elevated serum simvastatin by 3.6-fold (range 1.8-6.0 fold); however, no significant changes were detected in any pravastatin pharmacokinetic parameter examined when pravastatin was taken with grapefruit juice.[69-72]

Discussion

The growing use of herbal remedies has far exceeded the increase in available information on their benefits, adverse effects and drug interactions. Although compounds isolated from herbs have been shown to have important pharmacologic activities, but in some observations, actions of the herbs have been overestimated or underestimated. Moreover, both administrators and costumers have little-evidenced information on safety, effectiveness, and adverse effects of these herbs. In this regard, the increasing number of foods containing herbs has raised concerns at the food and drug administration (FDA).

Several herbs offer potential for cardiovascular conditions including hyperlipidemia, hypertension and congestive heart failure through a variety of mechanisms such as antioxidant, antiplatelet, fibrinolytic, anti-atherosclerotic, anti-hyperlipidemic, antiarrhythmic and vasodilatory actions.[73] The present study attempted to first review published evidence on the efficacy of herbs against hyperlipidemia as a potential coronary artery risk factor and after that it focused on some evidence on probable interactions between these herbs and anti-hyperlipidemic drugs, especially statins.[74,75] In first step and by reviewing all published manuscripts on beneficial effects of herbs on serum lipids level, 17 herbs were described to be effective on lipid profile as lowering serum triglyceride, total cholesterol, LDL-C as well as increasing serum HDL level. Some herbs such as celery could even affect the hepatic triglyceride concentrations. Although all shown herbs had similar target points on serum lipids, but the physiological affectivity mechanisms of drugs was widely different, including changes in lipid oxidation (basil, dill), induce of inhibiting lipid accumulation by lipid catabolism (blueberry), inhibition of lipid production (celery), Inhibition of adipocyte differentiation and lipogenesis (dandelion, grape, and green tea), reducing lipid peroxidation (evening primrose oil and ginger), activation of lipase enzymes (fenugreek), up-regulation of adiponectin expression in adipocyte cell (ginseng), and decrease in hepatic HMG-CoA reductase activity (nigella). In

fact, different parts of lipid metabolism pathways can be affected by various types of herbs. According to similar effects of chemical drugs on lipid metabolism process, interaction between these drugs and herbs is expectable. However, few studies were implemented to clear these interactions. Regarding drug-herb interaction, the interaction between some types of herbs and statins that are commonly used for improving hyperlipidemia has been considered. As previously shown, the herbal reaction towards different types of statins is varied so that grapefruit or pomegranate were interacted with only some types of statins, but not with all statin types. In this context, administration of herbal materials can lead to decreased absorption of statins or decreased the plasma concentration of these drugs. Simvastatin, pravastatin, and lovastatin are inhibitors of HMG-CoA reductase, the rate-limiting step in cholesterol synthesis.[9] Thus, any herbs involved in activation or inhibition of this enzymatic pathway can induce changes in drug absorption or catalysis.

Acknowledgments

This article has been derived from the Ph.D. thesis of the first author and financially supported by the research deputy of Shahrekord University of Medical Sciences, Iran.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Rouhi-Boroujeni H, Rouhi-Boroujeni H, Heidarian E, Mohammadizadeh F, Rafieian-Kopaei M. **Herbs with anti-lipid effects and their interactions with statins as a chemical anti-hyperlipidemia group drugs: A systematic review.** ARYA Atheroscler 2015; 11(4): 244-51.

Left ventricular dysfunction: Neither a matter of atherosclerosis nor an anomalous originated right coronary artery from left anterior descending artery

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Case Report

Abstract

BACKGROUND: Abnormal separation of right coronary artery (RCA) from the left coronary system is an extremely rare variation among coronary artery anomalies. The compressions on the anomalous route of this artery may lead to arrhythmia, chest pain, or left ventricular dysfunction or may enhance formation of atherosclerotic plaques.

CASE REPORT: Here, we have reported a patient presented with heart failure who had an anomalous atherosclerotic RCA originating from left anterior descending artery. Interestingly, neither the anomalous origin nor the atherosclerosis was the cause of the patient's problems and she suffered from a hypertensive cardiomyopathy.

CONCLUSION: This reminds that encountering an anomaly should not solely be interpreted as the cause of cardiac disease.

Keywords: Coronary Angiography, Left Ventricular Dysfunction, Coronary Vessel Anomaly

Date of submission: 27 Mar 2014, ***Date of acceptance:*** 14 May 2015

Introduction

Approximately, 1.3% of coronary angiograms show the presence of coronary artery anomalies (CAA).[1] Separation of the right coronary artery (RCA) from the left coronary system is an extremely rare variation. Presence of these anomalies mostly raises concerns about their mechanical compression in their abnormal route to their target tissues. This compression may lead to myocardial ischemia which manifests as arrhythmia, chest pain, or left ventricular (LV) dysfunction. This anomalous route would cause perturbation of blood flow within the artery, enhancing the formation of atheromatous plaques within these vessels. The atherosclerosis process in turn causes arrhythmia, chest pain, or LV dysfunction as well. Here, we have reported an anomalous atherosclerotic RCA originating from left anterior descending artery (LAD), while none of the two pathologies were the cause of the patients' symptoms.

Case Report

A 65-year-old lady referred to our hospital with a complaint of dyspnea. She was not a smoker and her past medical history consisted of hypertension and hyperlipidemia. On admission, physical examinations revealed an elevated jugular vein pressure accompanied by pulmonary rales up to two-thirds from the base of the lung. The patient was tachypnic (respiratory rate = 28) and blood pressure was 180/100 with a normal oral temperature (36.9 °C). Her electrocardiogram showed slight T-wave inversions in the leads V_2 through V_6 as well as leads I and aVL. Occasional ventricular premature complexes were also present (Figure 1). The cardiac troponin level was normal. Echocardiogram of the patient showed a LV ejection fraction (LVEF) of 23% without regional wall motion abnormalities with dilated LV and atrium. Presence of moderate amounts of mitral regurgitation and moderate concentric LV hypertrophy was also noticeable.

Since there was no past medical history of heart failure, we proceed with coronary angiography to exclude ischemic causes as the basis of her disease. Cannulation of the left main coronary artery (LMCA) displayed normal courses of the LMCA, left circumflex (LCX), and LAD. An anomalous RCA as a separate large branch arose from the proximal area of LAD. The abnormally originated

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RCA had three significant stenoses in the proximal and distal portions (Figure 2A-C). Attempts to cannulate the RCA with the right Judkins catheter were unsuccessful. Aortography did not show the presence of another origin for a supplementary RCA from another site (Figure 2D). This was concluded to be a benign anomaly with an atherosclerotic disease. As the amount of LVEF impairment was not concordant with the epicardial coronary abnormalities, the patient was considered as a case of dilated cardiomyopathy and the patient was given long-term medical therapy for her heart failure as well as her atherosclerotic disease. At follow-up, it was observed that the patient had an asymptomatic clinical status.

Discussion

Disorders in the development of coronary arteries during the 3rd week of fetal development may eventually lead to CAAs. These disorders are discovered in 0.6-5.6% of diagnostic coronary angiograms, and in approximately 1% of routine autopsy examinations.[1] The most common CAA is the presence of separate ostias for the LAD and LCX, seen in 0.41% of angiograms, followed by separation of the LCX from the RCA with a prevalence of 0.37%.[2] An anomalous RCA originating from the left coronary (left sinus of Valsalva, the posterior sinus of Valsalva, the ascending aorta, the pulmonary artery, the LV, the LMCA, the LCX, or the LAD) system can be found in 0.1-0.9% of patients.[3] Origination of RCA from the LAD is extremely rare and in most of them, anomalous RCA stems from the proximal or mid-segment of the LAD.[4-7]

The separation of RCA from the LAD is usually a benign disorder which does not lead to coronary mal-perfusion.[8,9]

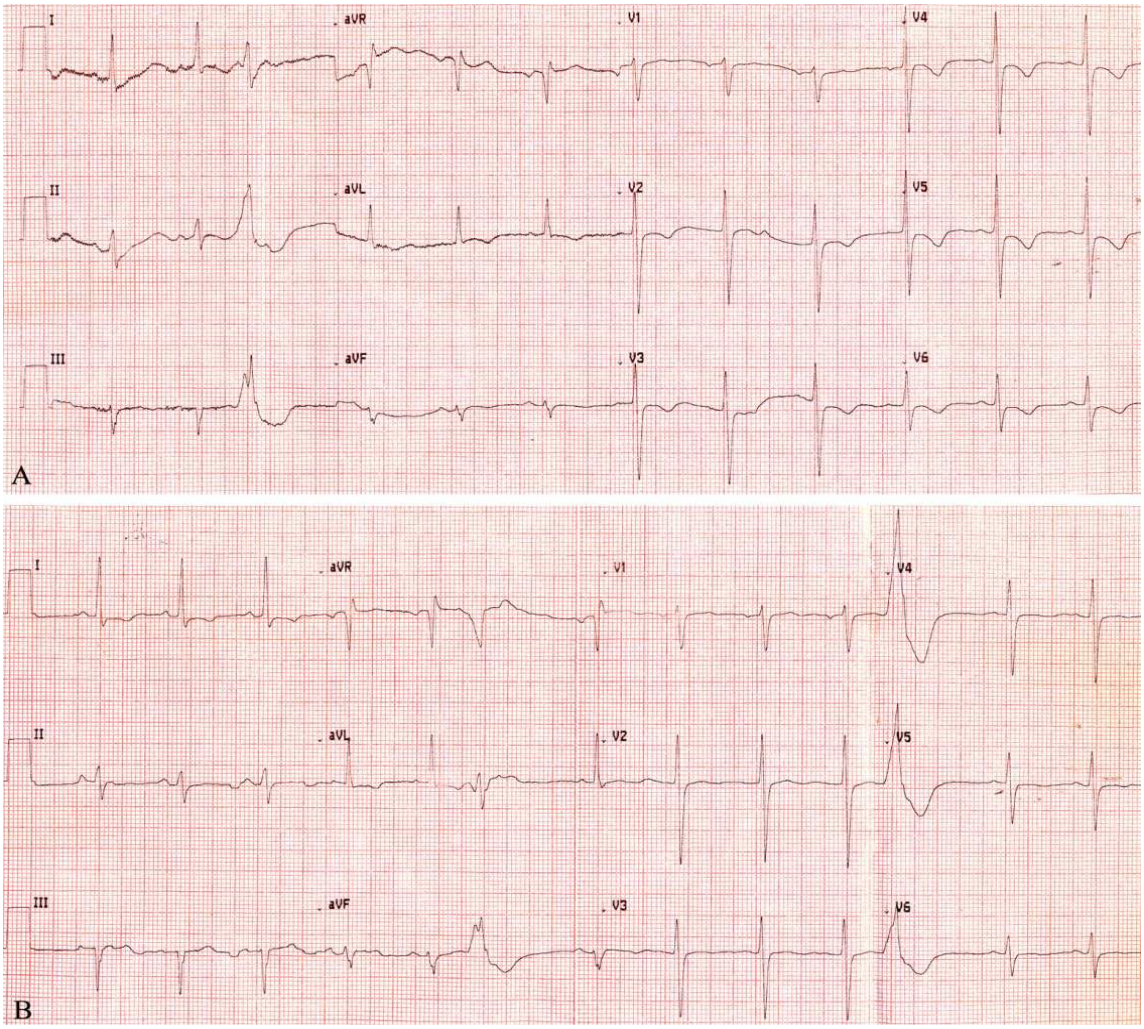

Figure 1. The electrocardiogram on admission showed slight T-wave inversion in the leads V_2 through V_6 as well as leads I and aVL with frequent ventricular premature complexes

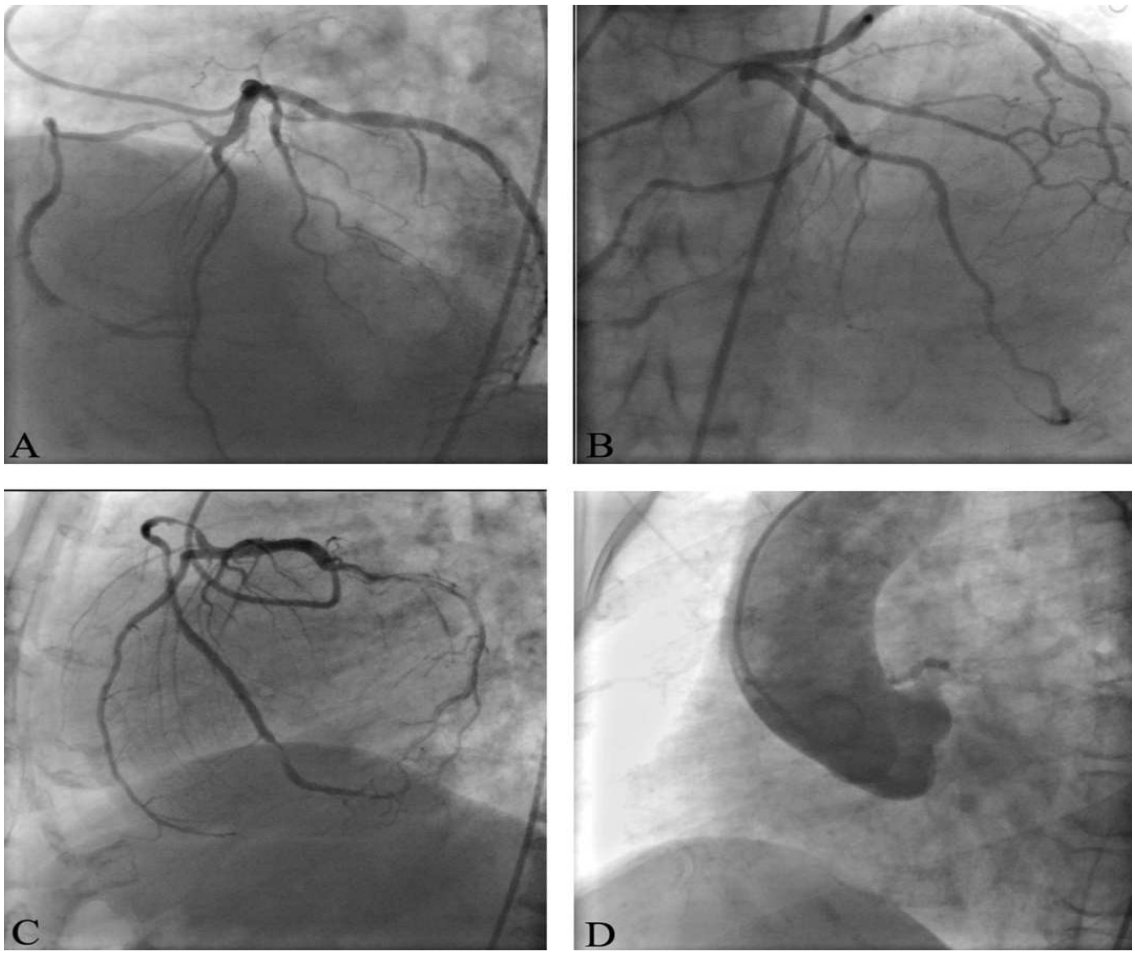

Figure 2. The coronary angiogram showed normal left main coronary artery, left circumflex, and left anterior descending artery (LAD); An anomalous right coronary artery (RCA) as a separate large branch arose from the proximal side of LAD; The abnormally originated RCA had three significant stenoses in the proximal and distal portions visible in the: (A) Left anterior oblique view with cranial angulation, (B) right anterior oblique view with cranial angulation, (C) Left lateral view, and (D) Aortography did not show the presence of an origin of a supplementary RCA from another site

The abnormal origin and course of these vessels may make them more prone to atherosclerosis which may lead to premature atherosclerotic stenosis within these vessels.[10] Most patients with this pathology suffer from an exertional angina. However, other there would be other manifestations such as lethargy, hoarseness, and epigastric pain.[4-6] Here, we have reported a case that summons the anomalous origin of RCA from LAD and atherosclerotic changes in that vessel. The absence of chest pain in this patient may be related to partial immobility of patient secondary to her heart failure. Furthermore; this absence of chest pain can be contributed to the well-developed collaterals from LCX supplied the distal portion of RCA as well.

In this patient, the amount of LV dysfunction could not be explained by a single inferior wall ischemia secondary to RCA disease state. So, none of the two pathologies led to her symptoms and she suffered from a third irrelevant disease, dilated cardiomyopathy, possibly due to longstanding hypertension. Hence, it is important to once encounter an anomaly, not solely interpret the concomitant cardiac problems as a consequence of that anomaly.

Acknowledgments

The authors would like to thank Dr. Nasrin Shokrpour at Center for Development of Clinical Research of Nemazee Hospital, Shiraz, Iran, for editorial assistance.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Attar A, Rezaee M, Kheirkhah J. **Left ventricular dysfunction: Neither a matter of atherosclerosis nor an anomalous originated right coronary artery from left anterior descending artery.** ARYA Atheroscler 2015; 11(4): 252-5.

Influence of nandrolone decanoate administration on serum lipids and liver enzymes in rats

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Short Communication

Abstract

BACKGROUND: Anabolic-androgenic steroids have been associated with several side effects range. This experimental study was conducted to evaluate the effects of nandrolone decanoate (ND, an anabolic steroid) on lipid profile and liver enzymes in rats in Iran.

METHODS: Forty adult male and female of Wistar strain rats were randomly assigned to four groups of 10 animals each: male control, female control, ND-male treated (15 mg/kg b.w./day), and ND-female treated (15 mg/kg b.w./day). Serum concentrations of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were measured in all studied groups.

RESULTS: Treating rats with ND (case group) resulted in a significant elevation of TC (69.4 ± 8.7), TG (101.6 ± 32.9) and ALT (72.2 ± 13.8) and significant reduction of LDL (6.4 ± 2.6) and AST (138.7 ± 19.4) as compared to control group in female rats. ND supplementation (case group) significantly increased TC (64.4 ± 6.2), AST (255.0 ± 32.0), and ALT (84.3 ± 3.8) in comparison with the control group in male rats.

CONCLUSION: Overall, our result indicated that the ND use can cause a negative effect on lipid profile and liver enzyme in rats.

Keywords: Aspartate Aminotransferase, Nandrolone Decanoate, Rat, Steroids

Date of submission: 22 Jan 2014, ***Date of acceptance:*** 25 Apr 2015

Introduction

During the past decades, the naturally occurring hormone testosterone and its synthetic derivatives [collectively termed anabolic androgenic steroids (AAS)] have been used by athletes, bodybuilders, and youths in order to increase muscle mass or enhance physical endurance.[1-4] The AAS are a family of lipophilic hormones derived from cholesterol that includes the natural male hormone, testosterone, together with numerous synthetic testosterone derivatives.[5] AAS are used in medical clinics as well as with the purpose to improve physical performance of individuals submitted to physical training.[6] Although AAS have valid medicinal uses, nontherapeutic abuse also occurs.[7,8] Recent increases in androgen prescriptions are evident.[9,10] Some of the common orally administered AAS include nandrolone decanoate (ND), oxymetholone, oxandrolone, and stanozolol.[11] ND is frequently used to treat many diseases such as human immunodeficiency virus-associated muscle wasting,[12] prostate cancer and benign prostate hyperplasia, and well-known androgen-dependent diseases.[13] However, despite such therapeutic beneficial potentials, chronic, and unregulated use of ND result in undesirable outcomes, including hepatic toxicity,[14] alteration of thyroid function,[15] cardiovascular toxicities.[16] Many studies concluded that androgen therapy is associated with high incidence of adverse effect in lipid profiles,[17] while others have shown that ND has no marked effect on the lipid profile.[18] In the study by Ghorbanihaghjo et al.,[19] treatment with ND was affected in total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and liver enzymes in rats.[17]

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In regard to the importance of knowing ND effects on liver and heart and inconsistent results of previous studies in this context, the present study aimed to assess the ND effects on lipid profile and liver enzymes in rats.

Materials and Methods

This experimental study was performed in Zahedan University of Medical Sciences, Iran, at 2009. It was used forty adult male and female of Wistar strain weighing 180 ± 30 g. Rats purchased from the Pasteur Institute in Tehran, Iran.

The animals were housed in air-conditioned room maintained at 22 ± 2 °C, with a relative humidity of 50 ± 10% and a 12 hours light/dark cycle with free access to food (commercial rat chow: Pars Animal Feed Co., Tehran, Iran) and water.

This study was approved by the Ethics Committee of the Zahedan University of Medical Sciences under approval No. 1230 at 2009.

ND was prepared from Caspian Tamin Pharmaceutical Company (Guilan, Iran). The rats were randomly assigned to four groups of 10 animals each: male control, female control, ND-male treated (15 mg/kg b.w./day), and ND-female treated (15 mg/kg b.w./day).[20-22] Duration of each treatment was 8 weeks.

Blood was withdrawn to estimate biochemical factors from the animals under ether anesthesia. The equipment was previously calibrated. Samples were maintained for 40 minutes at laboratory temperature and then centrifuged (1000 g for 15 minutes) to separate serum.[23] Lipid profile (mg/dl) [TC, TG, LDL-cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)], and liver enzymes (U/L) [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] were assayed using routine enzymatic methods (Pars Azmoon, Tehran, Iran) on an automated chemistry analyzer (Hitachi Model 902, Tokyo, Japan). All experiments were carried out in Zahedan University of Medical Sciences.

Statistical analyses were conducted using SPSS software for Windows (version 13, SPSS Inc., Chicago, IL, USA). The student t-test was used to compare mean values between groups. The results were expressed as mean ± standard deviation. A $P < 0.050$ was considered as statistically significant.

Results

Effect of ND on serum concentrations of lipid profile parameters and liver enzymes in female and male groups are provided in table 1. Treating rats with ND resulted in a significant elevation of TC (69.4 ± 8.7), TG (101.6 ± 32.9), and ALT (72.2 ± 13.8), and significant reduction of LDL (6.4 ± 2.6) and AST (138.7 ± 19.43) as compared to control group in female rats. In contrast, the serum concentrations of HDL-C were statistically unchanged after the ND consumption in female group.

ND administration significantly increased TC (64.4 ± 6.2), AST (255.0 ± 32.00), and ALT (84.3 ± 3.8) in comparison with the control group, while there was no statistically significant difference in other factors (TG, LDL-C, and HDL-C) in male rats.

Discussion

Among the various anabolic steroids available, ND is presented as one of the most used.[24] Evidence from the current study indicated a trend toward increase of the TC, TG, and ALT and decline of the HDL-C in female rats and enhancement of the TC, AST, and ALT in male rats after ND consumption.

Table 1. Effects of nandrolone decanoate on serum concentrations of lipid profile parameters and liver enzymes in experimental groups

Gender	Group (n = 40)	Total cholesterol (mg/dl)	Triglyceride (mg/dl)	Low-density lipoprotein (mg/dl)	High-density lipoprotein (mg/dl)	Aspartate aminotransferase (U/L)	Alanine aminotransferase (U/L)
Female (n = 20)	Control	56.1 ± 7.9	77.1 ± 17.2	12.6 ± 6.6	43.6 ± 4.4	169.8 ± 37.70	59.8 ± 9.9
	Case	69.4 ± 8.7	101.6 ± 32.9	6.4 ± 2.6	42.6 ± 4.9	138.7 ± 19.43	72.2 ± 13.8
	P	0.020	0.050	0.020	0.640	0.030	0.020
Male (n = 20)	Control	54.1 ± 11.4	67.2 ± 15.4	9.2 ± 7.1	44.1 ± 4.2	169.7 ± 4.24	71.6 ± 8.9
	Case	64.4 ± 6.2	64.4 ± 16.1	7.9 ± 3.9	44.7 ± 4.8	255.0 ± 32.00	84.3 ± 3.8
	P	0.020	0.680	0.670	0.770	0.001	0.010

Student t-test was used to compare mean values between groups; P values are significant $P < 0.050$

Among the many toxic and hormonal effects of AAS that have been documented, attention has been turned recently to the increased levels of TC and LDL-C and decreased levels of HDL-C.[25,26]

Although the results of the AAS effect on TC levels are conflict. Some studies have found that repeated supraphysiologic doses of AAS are associated with an increase in TC levels,[27] whereas others have failed to find such an association.[28] The reason for the discrepancy observed in the effect on TC after AAS administration may be the different study designs used, sampling time, type of AAS used, administration route, etc.[29]

In our study, ND was used and had an undesirable effect on TC levels.

Some studies comment that submaximal exercise induces an increase in hepatic lipoprotein lipase, which in turn leads to enhanced TG clearance and probably decreases plasma clearance of HDL constituents.[30]

In the Gold et al.,[31] study in human immunodeficiency virus (HIV)-positive males, no significant differences were detected between the placebo and ND groups (150 mg) for changes in serum cholesterol (total, LDL or HDL), and TG whereas in our study, significant differences were observed in these factors in female group and TC in male group.

Also finding of Hartgens et al.,[28] and Sattler et al.[32] study are inconsistent with our results. Hartgens et al.,[28] found, ND (200 mg/week) did not influence serum TG, TC, HDL-C concentrations after four and 8 weeks of intervention. Sattler et al.[32] illustrated no detrimental effects of ND on TG, or TC or LDL-C. HDL-C reduced transiently during ND treatment, but returned to near-baseline levels when assessed 12 weeks after the treatment was finished.

There is a broad variability among the results of the several human and animal studies on the hepatic injury, as well as on the criteria used to categorize the severity of hepatotoxicity.[33] The determination of serum transaminase levels is generally considered to be of great value to detect toxic effects on the liver.[34] However, the misinterpreted idea that the increase of only one hepatic enzyme could represent liver toxicity is frequently observed, when the ideal interpretation should be made using two or more hepatic enzymes.[35] In our study, we found increased levels of two important enzymatic markers of the liver toxicity, demonstrating that ND treatment can lead to a state of hepatotoxicity.

There are much molecular evidences to suggest that AAS acts by activating genes related with the synthesis of liver enzymes.[35] Gene alterations and/or epigenetic factors provoked by the use of AAS may be linked with hepatocellular dysfunction.[36]

Hough[37] expressed, increase levels of AST, ALT, and lactate dehydrogenase are common in athletes who use steroids.

Vieira et al.,[38] reported that ND administration leads to a dose-dependent increase in serum levels of the AST, ALT, and alkaline phosphatase in rats. These results suggest that subchronic treatment with ND, mainly administered at higher-than-clinical doses, are potentially deleterious to the liver, leading to incipient fibrosis.

The strong point of our study was sample size. 10 rats in each group decrease rate of error. The using of several doses of ND was better in this study.

With regard to the observed undesirable effects of ND, future human studies on people who take ND are greatly recommended to investigate side effects of ND and optimal dose of it.

Conclusion

Our result indicates that ND caused negative effects on lipid profile and liver enzymes in rats.

Acknowledgments

This study was extracted from a thesis by Fatemah Sameinasab. The authors gratefully acknowledge the authorities at the Zahedan University of Medical Sciences for financial support of this study.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Samieinasab MR, Shahraki MR, Samieinasab F, Najafi S. **Influence of nandrolone decanoate administration on serum lipids and liver enzymes in rats.** ARYA Atheroscler 2015; 11(4): 256-60.

Effect of peroxisome proliferator-activated receptor γ on inflammatory markers

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Letter to Editor

Date of submission: 4 Jan 2015, ***Date of acceptance:*** 4 Apr 2015

Introduction

In a recent study published in "ARYA atherosclerosis," Pourmoghaddas et al. reported that administration of pioglitzone in non-diabetic patients with metabolic syndrome had no positive effect on inflammatory markers including high sensitive C-reactive protein, interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α).[1]

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors which involved in some physiological processes including energy balance, lipid metabolism, and glucose control.[2] They improve glycemic control and enhances insulin sensitivity in diabetic patients.[2,3] These drugs also improve the lipid profile of patients at risk of developing atherosclerosis.[4] PPAR-γ has been implicated in the pathology of numerous diseases including atherosclerosis, obesity, diabetes, and cancer because of its role in modifying adipocyte differentiation, decreasing insulin resistance, and inhibiting vascular endothelial growth factor-induced angiogenesis.[5]

PPARs have three isotypes: PPAR-α, PPAR-γ, and PPAR-ß/δ. There are four isoforms of PPAR-γ in the human. PPAR-γ 1 is found in almost all tissues and PPAR-γ 2 found in adipose tissue.[3,6] PPAR-γ 3 is found in adipose tissue, colon, macrophages, and T-lymphocytes.[6] There are currently no information regarding the distribution of PPAR-γ 4.[6]

The effect of PPAR-γ agonists on inflammatory markers is complex. Although, several in vivo and in vitro studies reported the anti-inflammatory effect of these drugs, however, the complexity of the pro- and anti-inflammatory PPAR-γ functions have also been observed. Several mechanisms for anti-inflammatory action of PPAR-γ are proposed: (1) inhibition of metalloproteinases expression and activity for example metalloproteinase-9 expression in atherosclerotic plaques.[6] (2) Repression the expression of several inflammatory response genes (iNOS, TNF-α,…) in activated macrophages,[7] TNF-α, plasminogen activator inhibitor-1, and IL-6 expression in adipose tissue[8] or TNF-α, IL-6, and IL-1 in human monocytes.[7] (3) Reduction of transcriptional activities (nuclear factor-κB, AP-1, and STAT) or inability of these factors to bind to the iNOS promoter in monocytes.[6] (5) Suppression the lipopolysaccharide (LPS)-induced TNF-α in human alveolar macrophages.[9]

However, other studies demonstrated that PPAR-γ ligands induce certain pro-inflammatory responses. They induce macrophage differentiation and upregulate the macrophage pro-inflammatory surface receptors (such as CD14, CD11/CD18, and scavenger receptor B1).[6] 15-Deoxy-Delta-12,14-prostaglandin J2 (15d-PGJ2), a PPAR-γ agonist, induces expression of IL-8 and at the same time suppresses the expression of monocyte chemoattractant protein-1.[10] In another study, rosiglitazone did not have effect on LPS-induced IL-8, but it suppressed matrix metalloproteinase-9.[11] Therefore, it seems that the effect of PPAR-γ ligands on the inflammatory response is complex and depend upon the mediators that are measured, PPAR-γ ligand used and its concentration and the activation state of the target cell.[6,12]

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Khazaei M. **Effect of peroxisome proliferator-activated receptor γ on inflammatory markers.** ARYA Atheroscler 2015; 11(4): 261-2.

Retracted: Pulmonary hypertension due to a pulmonary artery Leiomyosarcoma: A case report

ARYA Atherosclerosis

Retraction

The article titled "Pulmonary Hypertension due to a Pulmonary Artery Leiomyosarcoma: A Case Report."(1), published online on March 2014 in ARYA Atherosclerosis Journal, and in Volume 10, pp. 133-136, has been retracted by the Editor-in-Chief of this journal. The decision was made due to duplicate submission of the manuscript by the same authors in "Seyyed Hassan Adeli, Bardia Nemati, Mahboubeh Jandaghi, Mohammad Mahdi Riahi, Fatemeh Hosseinzadeh, and Fatemeh Salarvand. Pulmonary Hypertension due to a Pulmonary Artery Leiomyosarcoma: A Case Report. Case Rep Pulmonol. 2013; 2013: 160619".

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